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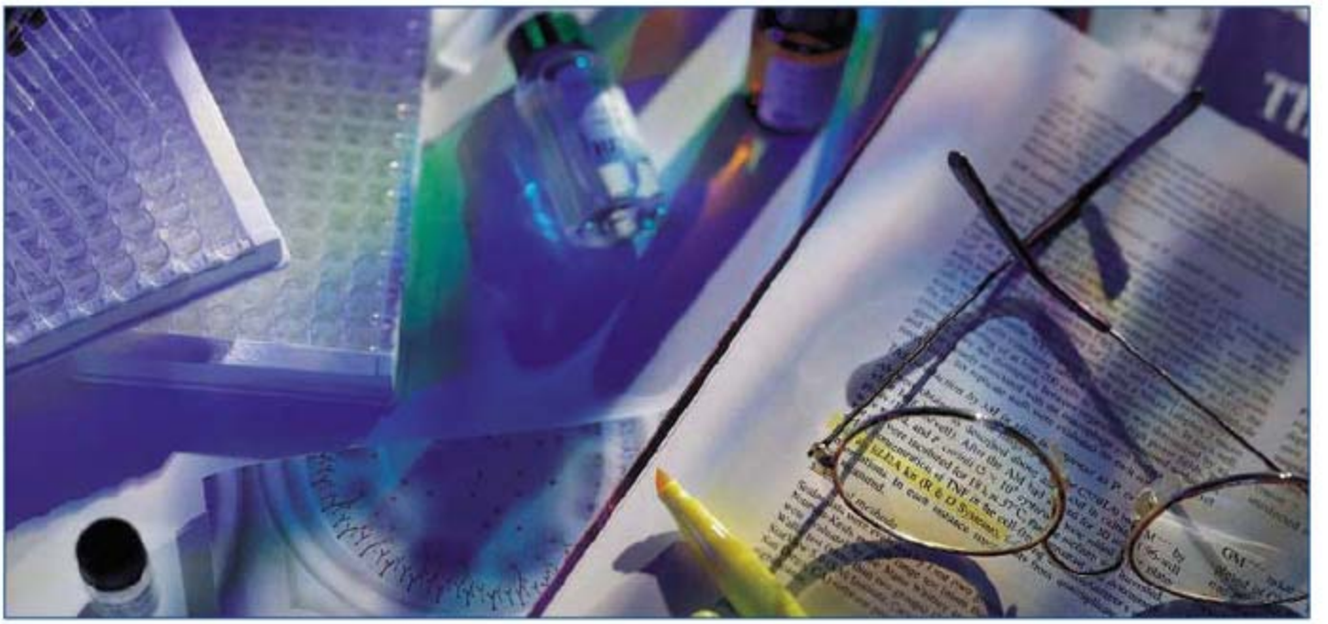

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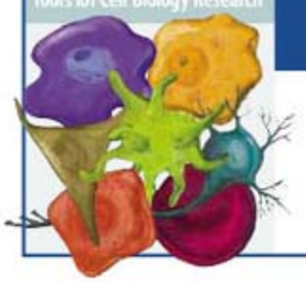

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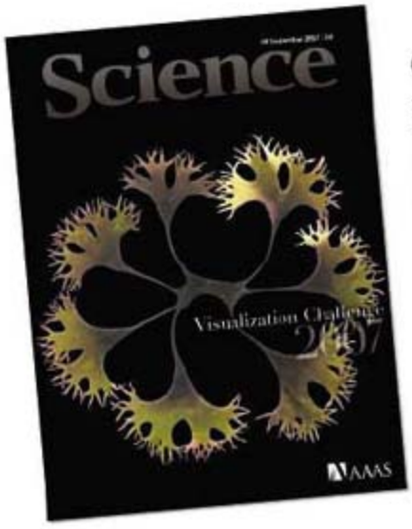


COVER

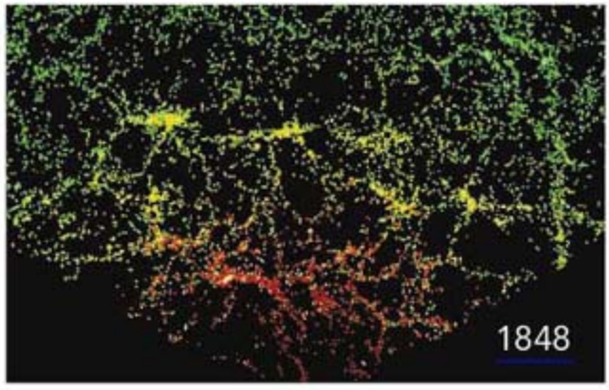
The red alga *Chondrus crispus* (Irish moss). This image, taken with a digital point-and-shoot camera, tied for first place in the photography category of the National Science Foundation/*Science* 2007 Visualization Challenge. All the winning entries are displayed in a special feature beginning on page 1857 and online at www.sciencemag.org/sciext/vis2007.

Image: Andrea Ottensen

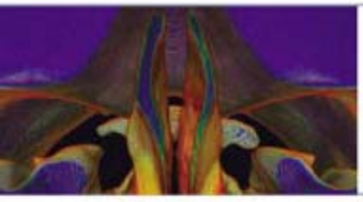
DEPARTMENTS

EDITORIAL

NEWS OF THE WEEK



NEWS FOCUS



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BOOKS *ET AL.*

1869

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PERSPECTIVES

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GENETICS

Paired-End Mapping Reveals Extensive Structural Variation in the Human Genome

J. O. Korbel et al.

Sequencing of structure variations over segments of DNA from two individuals of different ethnic groups showed unexpected levels of diversity.

10.1126/science.1149504

GENETICS

Wasp Gene Expression Supports an Evolutionary Link Between Maternal Behavior and Eusociality

A. L. Toth et al.

Analysis of a set of genes expressed in the brain of a primitive wasp shows that the care shown by worker wasps toward siblings probably evolved from maternal care behavior.

10.1126/science.1146647

CLIMATE CHANGE

Southern Hemisphere and Deep-Sea Warming Led Deglacial Atmospheric CO_2 Rise and Tropical Warming

L. Stott, A. Timmermann, R. Thunell

Dating of benthic versus near-surface plankton in a Pacific Ocean core shows that southern high latitudes warmed 1500 years before the tropics during the last deglaciation.

>> *News story p. 1847*

10.1126/science.1143791

ASTRONOMY

A Bright Millisecond Radio Burst of Extragalactic Origin

D. R. Lorimer, M. Bailes, M. A. McLaughlin, D. J. Narkevic, F. Crawford

A rapid and powerful burst of radio waves is found through an analysis of archival pulsar data, suggestive of a new class of radio bursts, perhaps from a supernova.

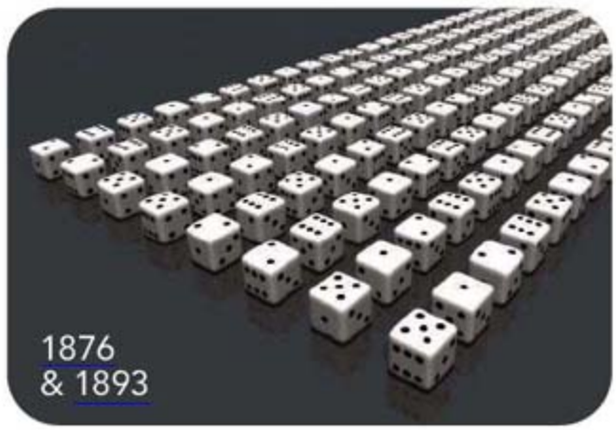
10.1126/science.1147532

TECHNICAL COMMENT ABSTRACTS

REVIEW

BREVIA

REPORTS



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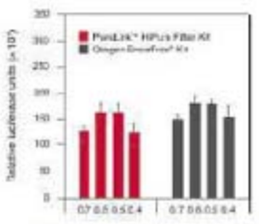

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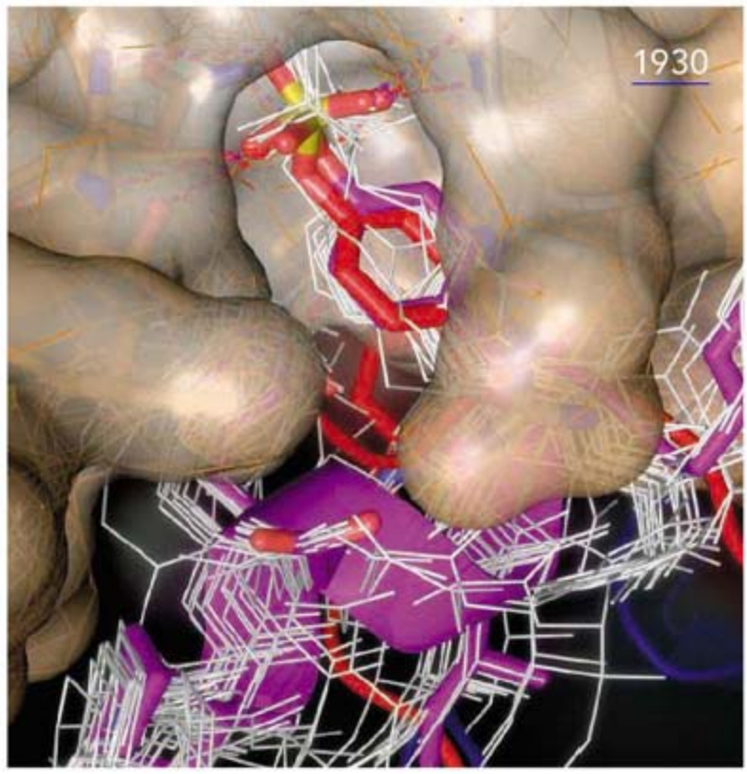

CREDIT: JOHNATHAN STUCKEY, VACCINE RESEARCH CENTER, NIAID, NIH

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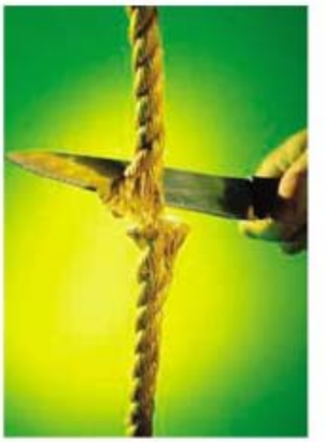
D. Pfaff and R. Silver
The effects of estrogen on behavior are modulated by day length.

PROTOCOL: Studying Integrin-Mediated Cell Adhesion at the Single-Molecule Level Using AFM Force Spectroscopy
C. M. Franz, A. Taubenberger, P.-H. Puech, D. J. Muller
Forces between adhesion receptors and their ligands can now be measured at the level of single molecules.

GLOSSARY
Find out what Smo, Ptc, and Gas1 mean in the world of cell signaling.



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B. Noordam and P. Gosling
Here are some tips for getting a progress review with the answers and a plan you need.

MISCINET: Educated Woman, Postdoc Edition, Chapter 9—The Postdoc Has Two Faces
M. P. DeWhyse
Micella attempts to figure out how to make it through the next 2 months without her head splitting.

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J. Austin
Writing an effective research plan is an important part of your development as a scientist.

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Edison T. Liu and William N. Hait, Chairpersons
Singapore

November 14-17, 2007
Advances in Colon Cancer Research
Monica M. Bertagnolli, Hans Clevers, and Raymond N. DuBois, Chairpersons
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In conjunction with the AACR Minorities in Cancer Research Council
John D. Carpten, Timothy R. Rebbeck, and Olufunmilayo I. Olopade, Program Committee Chairpersons
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December 5-8, 2007
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Andrew J. Dannenberg, Program Committee Chairperson
Philadelphia, Pennsylvania

December 6-9, 2007
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January 22-25, 2008
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February 3-5, 2008
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Rakesh Kumar and Alan Hall, Chairpersons
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February 12-15, 2008
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John E. Dick and Jane Visvader, Chairpersons
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February 24-26, 2008
Energy Balance and Cancer: Mediators and Mechanisms
Joint AACR-Transdisciplinary Research on Energetics and Cancer (TREC) Conference
Nathan A. Berger, John D. Potter, Kathryn H. Schmitz, and Cornelia M. Ulrich, Chairpersons
Lansdowne, Virginia

March 15-18, 2008
Advances in Cancer Research: From the Laboratory to the Clinic
Samir N. Khleif, Chairperson
Dead Sea, Jordan

April 12-16, 2008
AACR Annual Meeting
Eileen P. White, Program Committee Chairperson
San Diego, California

May 20-23, 2008
Candidate Pathways, Whole Genome Scans: Reconciling Results, Looking into the Future
In conjunction with the Molecular Epidemiology Working Group of the AACR
Cornelia M. Ulrich and Stephen Chanock, Chairpersons
Carefree, Arizona

May 28-31, 2008
Cancer Epigenetics
Jean-Pierre Issa and Peter W. Laird, Chairpersons
Boston, Massachusetts

July 21-24, 2008
AACR Centennial Conference: Translational Cancer Medicine
Chairperson TBD
Monterey, California

August 3-7, 2008
Joint Metastasis Research Society-AACR Conference on Metastasis
Danny R. Welch, Chairperson
Vancouver, British Columbia, Canada

Fall, 2008
Omics to Clinics: Translation of Cancer Genome Insight Into Therapeutics and Diagnostics
Lynda Chin, Joe W. Gray, William R. Sellers, and Richard L. Schilsky, Chairpersons
Location TBA

October 13-17, 2008
Chemical and Biological Aspects of Inflammation and Cancer
Michael Karin, Lisa M. Coussens, and Lawrence J. Marnett, Chairpersons
Ko Olina, Oahu, Hawaii

October 21-24, 2008
EORTC-NCI-AACR International Conference on Molecular Targets and Cancer Therapeutics
Patrick Schöffski, James H. Doroshow, and Eric H. Rubin, Scientific Committee Chairpersons
Geneva, Switzerland

November 3-6, 2008
AACR Centennial Conference: Impact of Emerging Technologies on Cancer Diagnosis and Therapeutics
Michael B. Kastan, Joseph D. Rosenblatt, and Moshe Oren, Chairpersons
Jerusalem, Israel

November 11-14, 2008
Targeting the PI3-Kinase Pathway in Cancer Prevention
Lewis C. Cantley and Charles L. Sawyers, Chairpersons
Cambridge, Massachusetts

November 16-19, 2008
Seventh Annual International Conference on Frontiers in Cancer Prevention Research
Chairperson TBD
Washington, DC

December 2-5, 2008
Tumor Immunology
Louis M. Weiner, Olivera J. Finn, Alexander M. M. Eggermont, and Dmitry I. Gabrilovich, Chairpersons
Miami, Florida

December 5-7, 2008
Infection and Cancer: Biology, Therapeutics, and Prevention
Anthony T.C. Chan, Chairperson
Waun Ki Hong, Honorary Chairperson
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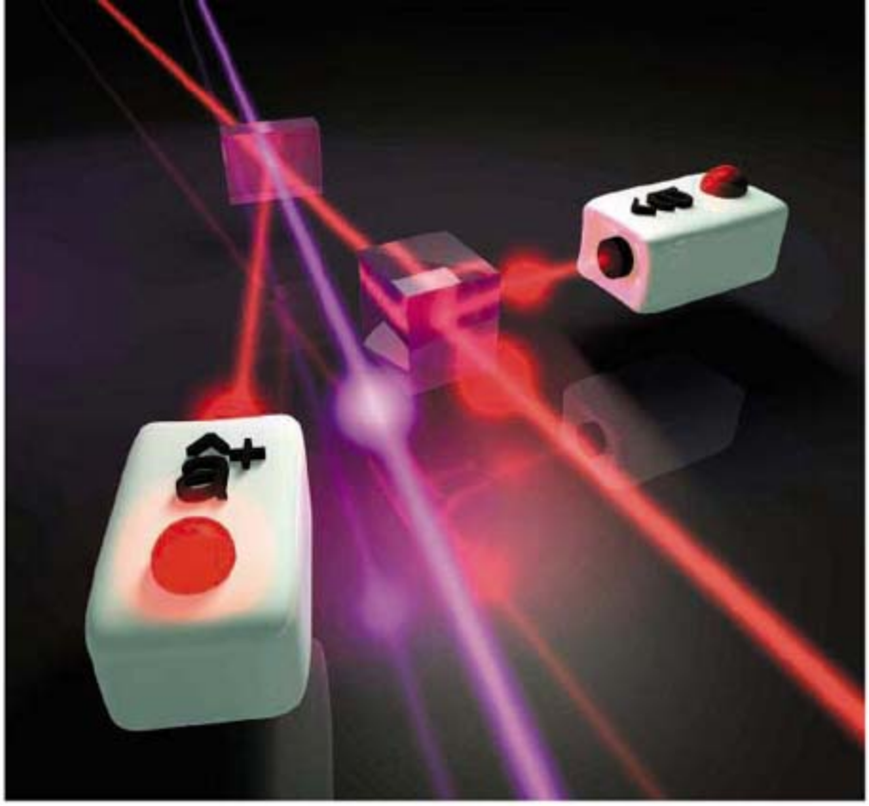

When Quantum Arithmetic Doesn't Add Up

If you add an item to your shopping basket and then remove one that is identical, your total bill does not change. If you shop in a quantum supermarket, however, the probabilities and the sequence of adding or subtracting to your shopping basket matter and can change the total. **Parigi *et al.*** (p. 1890; see the Perspective by **Boyd *et al.***) demonstrate this counterintuitive behavior for photons in a light field. Adding or subtracting a single photon to or from a light field produces a different result depending on the sequence of the event, with the final state of light field being different from the initial one. This capability of engineering the quantum state of a light may prove useful in areas such as quantum communication.

Fluorinated Drugs on the Rise

Organofluorine substituents are playing an increasingly important role in synthetic small molecule pharmaceuticals, including such major drugs as Lipitor and Prozac. In a review, **Müller *et al.*** (p. 1881) highlight the emerging understanding of how fluorine interacts with proteins during docking events. Elucidation of these intermolecular interactions complements more traditional paradigms of fluorine's electron-withdrawing effects, which influence substrate basicity, and its wide-ranging stereoelectronic impact on substrate conformation. The discussion is supported by analysis gleaned from extensive searches of structural databases.

Quantum Noise Reduction

A successful quantum computer must overcome decoherence effects caused by interactions with its environment. Such effects could be mitigated if they fully characterized, which in principle can be done by process tomography. However, this process requires resources that grow exponentially with the number of qubits in the system, which renders it impractical. **Emerson *et al.*** (p. 1893; see the Perspective by **Bacon**) describe a theoretical technique through which key features of the decoherence can be efficiently measured, which reduces the number of experiments from exponential to polynomial. The authors present an experimental implementation of the method on quantum-information processors based on liquid-state and solid-state nuclear magnetic resonance methods.

Up in the Air

Widespread free oxygen is thought to have evolved in Earth's atmosphere only after about 2.4 billion years ago. Candidates for the cause of increase include dynamic effects in the planet's interior, escape of hydrogen, or the evolution of cyanobacteria. **Anbar *et al.*** (p. 1903) and **Kaufman *et al.*** (p. 1900) examined the geochemistry of a detailed section obtained in a drill core through the Mount McRae Shale, Western Australia, dated to about 2.5 billion years ago. They used trace element chemistry (particularly of molybdenum and rhenium, which respond to oxidative weathering) and the mass-independent fractionation of sulfur isotopes (which can indicate the lack of abundant ozone) to trace the presence of free oxygen. The data indicate the first hints of atmospheric oxygen, but still at low levels, at this time.

Seen On Edge

In a rare alignment, the plane of Uranus' rings appeared edge-on to Earth in August 2007. This unusual configuration reveals the unlit side of the rings, including faint rings that are brightened by scattered light. With the Keck telescope in Hawaii, **de Pater *et al.*** (p. 1888, published online 23 August) snapped an infrared picture of the side-on rings. Diffuse dust envelops the entire ring system but is unconnected with any particular ring or feature. The pattern of dust has changed significantly since the rings were first photographed by the Voyager spacecraft in 1986, which indicates that such changes are common in the solar system and occur on much larger scales than had been expected.

Spin, All Together Now

Manipulation of the spin of an electron in a single quantum dot is a strong contender for quantum-information processing protocols. However, the spin dynamics of each dot depend strongly on environment, and the distribution resulting from dot-to-dot variability presents a formidable problem in addressing a system with many quantum dots. **Greilich *et al.*** (p. 1896) report on femtosecond magneto-optical pump-probe experiments on an ensemble of self-assembled semiconductor quantum dots. A sequence of laser pulses can induce all of the electronic spins across the ensemble to precess coherently. As the spin information is stored in the nuclear spin, this process effectively results in a long-term memory for the electronic phase information.

Hawaiian Getaways

Some Polynesian legends describe voyages from Hawai'i back to other Polynesian islands, but

Continued on page 1831

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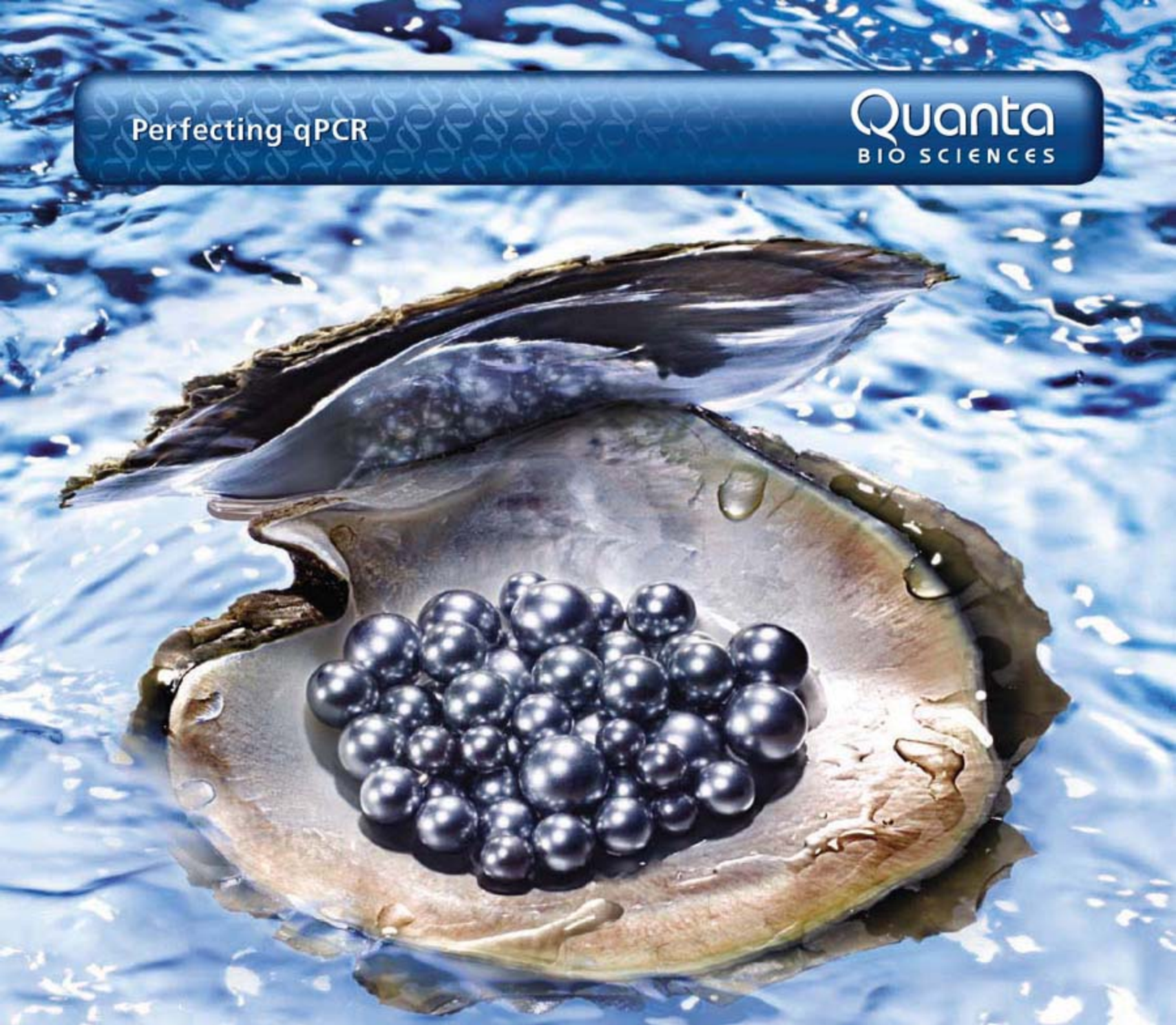

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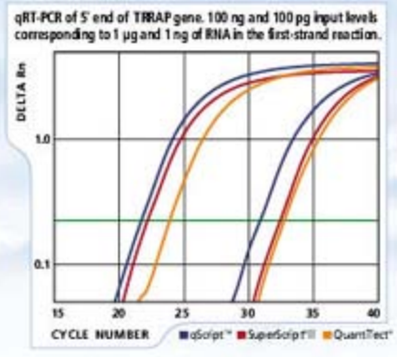

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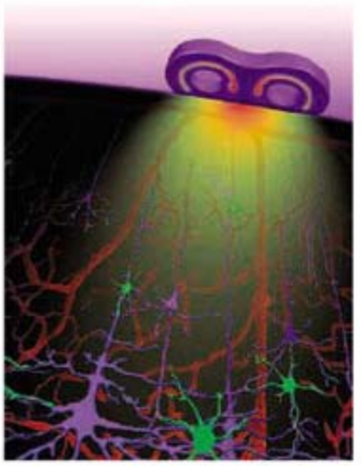
Continued from page 1829

evidence for these return trips has been lacking. **Collerson and Weisler** (p. 1907; see the Perspective by **Finney**) have examined the chemistry of 19 basalt adzes collected on a coral atoll in the Tuamotus to trace their origin. The data link many of the adzes to nearby islands, but the isotope and trace element chemistry uniquely links one to Hawai'i, 3400 kilometers away. Thus, the Polynesians had a maritime trade network extending over thousands of kilometers and some repeated contact with Hawai'i.

Viral Pesticide Resistance

Although insect resistance to chemical agents is well documented, there is little information on virus insecticides. Generally, these have been considered safe reagents, with little prospect of resistance developing in the host; however, resistance to the codling moth granulovirus has been observed in field populations. **Asser-Kaiser *et al.*** (p. 1916) now show that the resistance factor is a Z sex-linked feature. After selection, a population was isolated that was 10,000- to 100,000-fold more resistant to the virus challenge, which is considerably higher than the naturally resistant field strains.



CREDIT: ELENA ALLEN

Giving the Brain a Magnetic Massage

Transcranial magnetic stimulation (TMS) is an increasingly common technique used to selectively modify neural processing. Although TMS reportedly alters neural and hemodynamic activity, basic neurophysiological evidence for these effects is largely unexplored. **Allen *et al.*** (p. 1918; see the news story by **Miller**) applied TMS to anesthetized cats while measuring neural and hemodynamic activity simultaneously in a co-localized region of the neocortex, and provide quantitative data on the neural effects of TMS and how they relate to standard neuroimaging techniques. These results also provide insight into the mechanisms of brain plasticity that are thought to underlie long-lasting therapeutic effects of TMS.

Parasitic Evolutionary Oddity

Giardia is a common intestinal protozoan parasite and an important human disease agent. **Morrison *et al.*** (p. 1921; see the Perspective by **Keeling**) offer a genome analysis of *Giardia* that reveals a wealth of unusual attributes, including an extremely simplified metabolic capacity relating to its parasitic life-style; little DNA heterozygosity in a cell thought to lack a sexual cycle; functionally enigmatic amino acid insertions in otherwise conserved regions of proteins; an unusual actin cytoskeleton that lacks conventional myosin; and simplified DNA replication and RNA processing machinery.

Mammoth Mitochondrial Sequencing Effort

Ancient DNA survives well in hair, is found in copious quantities in cold environments, and can be decontaminated easily. **Gilbert *et al.*** (p. 1927) used these advantages to completely sequence the mitochondrial genomes of 13 Siberian woolly mammoths. One of the samples came from the Adams mammoth, which was found in 1799 and has been stored at ambient temperatures for the last 200 years. This finding will facilitate analysis of samples of organisms that can only be found in museums.

Sulfated Tyrosine and HIV Entry

In order for human immunodeficiency virus type 1 (HIV-1) to enter host cells, its envelope glycoprotein gp120 must bind to the host-cell surface receptor CD4 and to a co-receptor. An unusual post-translational modification, tyrosine sulfation, is important to the co-receptor interaction. **Huang *et al.*** (p. 1930) have investigated HIV-1 gp120 interactions with a sulfated N-terminal peptide from the co-receptor CCR5 and determined the crystal structure of a tyrosine-sulfated antibody in complex with gp120 and CD4. A conserved site in gp120 recognizes sulfo-tyrosine and might be a target for design of therapeutics.

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European Young Investigators

SCIENCE IS INTERNATIONAL, BUT ITS FUNDING AND ADMINISTRATION ARE USUALLY A matter for governments of nation states. In Europe, this balkanization leads to problems; perhaps the worst is finding peer reviewers when, in a small country, applicants for support may have few peers. Of course, the definition of "peer" is not always clear, and it can be difficult to identify real experts in a field unless one is in it. That creates a problem, because supporting anything less than superior research wastes taxpayers' money. In a small country, identifying quality depends on the fair and accurate opinions of foreign experts.

Having dealt successfully with this problem, a Europe-wide collaboration to fund basic research through a program called the European Young Investigators [(EURYI); www.esf.org/activities/euryi.html] has sent four cohorts of outstanding young European scientists into their posts with substantial research support since 2004. For better or worse, that program, which supported research ranging from theoretical physics to sociology, made its final appointments this year. The good news is that almost 100 investigators got grants of up to 250,000 euros per year for 5 years with no strings attached. An important question now is whether the European Research Council (ERC) will manage a similar program (Young Investigator Programme) with the same attention to the freedom and independence of young investigators that became a hallmark of EURYI.

The EURYI scheme was hatched by a roster of research councils from all over Europe, encouraged and administered by the European Science Foundation. Heads of the research councils wanted to promote European, rather than national, science and were concerned about career structures in the European Research Area. EURYI arrived when the Framework Programmes of the European Union (EU) were already in place, but the latter were not intended to support basic research. Rather, the EU awards are contracts, not grants, with milestones and deliverables that are more appropriate to engineering projects than to the foggy uncertainties of basic research. And European scientists have long complained about the application paperwork required for EU support. Really, the only mystery is why it took so long to set up a simple grant scheme such as EURYI to support young scientists.

A successful EURYI awardee had typically made an important discovery as a graduate student, made another as a postdoctoral fellow abroad, often in the United States, and then returned to Europe to set up a thriving laboratory. I chaired the Life Sciences and Medical Sciences selection process during EURYI's 4 years and was very heartened by what I saw: administrators, panelists, candidates, and their institutions all enthusiastically supporting the program's mission and structure (rigorous review by national and international panels), no matter where they came from.

EURYI's success was quickly evident from the growth of the award's prestige, the increase in the mutual trust of the participating organizations, and the scientific contributions of the EURYI scholars. Countries entered and left the program, some disappointed by their lack of success, but it was important—and a surprise—that there was no "juste retour" in the EURYI scheme. A nation could submit candidates for consideration in proportion to its financial contribution, but there was no guarantee that any of them would be successful.

What of the future? EURYI has ended because the ERC is now set up with similar aims and a larger budget. The 19 countries of EURYI are enlarged to the 27 of the EU. The 2000 applicants over 4 years of EURYI increased to 9000 in the first year of the ERC. That's a good sign. Administering these schemes is a lot of work, but well worth it. We must hope that the ERC's new program builds on the firm foundations of trust, fairness, consistency, and continuity that helped EURYI successfully transcend national boundaries. The ERC must allow young scientists in Europe the responsibility and freedom for independent discoveries and rightful credit. Giving young scientists independence is (alas) still not universal throughout Europe. The EURYI awards were, as my friend said, "In comparison to the regular EU grants, something that scientists really like." Is that so terrible?

– Tim Hunt

10.1126/science.1150256

CREDITS (TOP TO BOTTOM): VOLKER STEGER; JUPITER IMAGES

CLIMATE SCIENCE

Thin White Lines

The 100,000 or so ships that make up the global commercial and military fleet collectively travel billions of vessel-miles every year, producing a large fraction of the pollution contributed by fossil fuel burning in the transportation sector. In addition to the direct radiative effects of their emissions, caused by the light-scattering properties of the particles themselves, aerosols from the exhaust plumes can produce thin lines of very low clouds in the marine boundary layer, an example of the aerosol indirect effect. It has been shown that the local effects of these clouds can be large, up to 100 W/m^2 (for comparison, the average solar flux at the top of the atmosphere is about 340 W/m^2), but how large an influence they exert on the global albedo has been an unresolved concern. Schreier *et al.* analyzed a full year of satellite data derived from ENVISAT AATSR (Environmental Satellite Advanced Along-Track Scanning Radiometer) in order to estimate the size of the radiative forcing caused by ship tracks. They found that, contrary to fears arising from previous global model estimates, the global annual mean radiative forcing from ship tracks was small, 0.4 to 0.6 mW/m^2, and negligible compared to estimates of total net anthropogenic radiative forcing, 0.6 to 2.4 W/m^2. Thus, it seems that ship tracks are too inconsequential to affect the rate of anthropogenic global warming. — HJS

Geophys. Res. Lett. **34**, L17814 (2007).

MOLECULAR BIOLOGY

Regulation Revealed Under Stress

In most eukaryotic genes, the protein-coding sequences are interrupted by noncoding introns. These introns are removed from the pre-mRNA transcript by RNA splicing, a process that provides an additional and sometimes critical layer of gene regulation. Unlike more complex organisms, few genes in the yeast *Saccharomyces cerevisiae* contain introns. In those that do, the splice site sequences often conform to a strict consensus, making it unlikely that the use of alternative splice sites figures in the differential expression of genes. Intriguingly, though, ribosomal protein genes (RPGs)—components of the mRNA translation machinery—are the largest class of intron-containing genes.

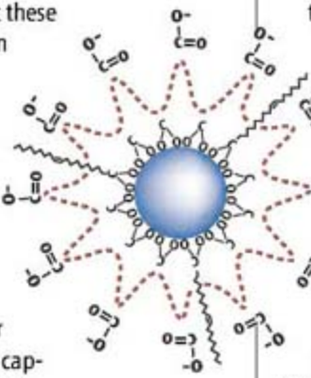
Pleiss *et al.* show that amino acid starvation, which induces a general repression of translation, also results in a rapid and specific reduction in the splicing efficiency of nearly all intron-containing RPG transcripts. This is not merely an effect of stressful circumstances, because exposure to high levels of ethanol does not have an effect on RPG splicing; rather the splicing of distinct sets of transcripts is either down- or up-regulated. The yet-to-be-discovered regulatory mechanisms, which other evidence suggests could be mediated by core, rather than accessory, spliceosomal components, probably explain the evolutionary retention of introns in these groups of yeast genes and, given the conservation of the RNA splicing machinery, similar mechanisms may pervade pre-mRNA splicing in higher eukaryotes. — GR

Mol. Cell **27**, 10.1016/j.molcel.2007.07.018 (2007).

CHEMISTRY

A Hot Dip Before Swimming

Most solution routes for nanoparticle synthesis proceed in nonpolar solvents and achieve size selectivity in part by capping the surfaces with hydrophobic groups. However, after this preparation, many applications require dispersing the nanoparticles in aqueous solvents. Ligand exchange reactions can be used to introduce capping agents that bear hydrophilic groups on their ends, but these reactions, which often run near room temperature, tend to be incomplete, and can lead to aggregation if ligand desorption dominates and exposes the underlying surfaces. Zhang *et al.* have developed a robust method for exchanging hydrophobic capping groups with short-chain polyelectrolytes such as poly(acrylic acid). The reactions run in polar solvent such as diethylene glycol with a high boiling point (in this case, ~245°C). The multivalent polyelectrolytes help displace the hydrophobic ligands while minimizing surface exposure. The properties of several nanoparticles—magnetism for iron oxides, photocatalysis for titanium dioxide, and photoluminescence for cadmium selenide—were maintained or even improved after such processing. — PDS



Nano Lett. **7**, 10.1021/nl071928t (2007).

PHYSICS

Stimulated Symmetry

Whereas the underlying parameters of condensed matter systems may be fixed, thereby limiting the phase space in which to vary the material properties, the ability to tune and manipulate atoms or molecules trapped in an optical lattice opens up that phase space. With success demonstrated already in systems with isotropic symmetry, as in the case of the superfluid–to–Mott-insulator transition of bosons on a square lattice, interest is now in describing systems with an anisotropic symmetry in the order parameter. Hemmerich and Morais Smith describe a scenario for imprinting a $d_{x^2-y^2}$ wave symmetry onto an array of polarizable bosons confined to a two-dimensional (2D) optical lattice. They show theoretically that exciting the atoms by stimulated Raman scattering can result in the formation of a checkerboard-like pattern of staggered flux states on adjacent plaquettes of the 2D lat-

CREDITS (TOP TO BOTTOM): GETTY IMAGES; ADAPTED FROM ZHANG *ET AL.*, *NANO LETT.* 7, 10.1021/NL071928T (2007)

tice, resulting in a *d*-wave momentum distribution. The proposed scenario offers the prospect of engineering optical lattices for the modeling of complex interacting phenomena from the likes of high-temperature superconductivity to magnetic frustration. — ISO

Phys. Rev. Lett. **99**, 113002 (2007).

BIOCHEMISTRY

Acquiring a Trace Element

Iron, as the central element in heme cofactors or as part of metal clusters, endows enzymes with the capacity to carry out a much wider range of redox reactions (such as those in respiration and photosynthesis) than is supported by the functional groups of the genetically encoded amino acids. Hence, the acquisition of iron is a highly competitive endeavor, and as ocean supplementation experiments have shown, iron can be a limiting nutrient for the growth of plankton. Nevertheless, marine organisms face a special challenge because iron in an aqueous and aerobic environment of neutral pH is present mostly in insoluble forms. The bacterial solution has been the manufacture and secretion of siderophores, small molecules that chelate Fe(III). Following on their previous identification of a borate-siderophore interaction, Harris *et al.* provide a fuller characterization of the equilibria in the reaction of $B(OH)_3$ and vibrioferrin, a siderophore of *Marinobacter* spp. The tetrahedral coordination of B(III) by the pair of α-hydroxycarboxylate moieties in vibrioferrin is highly pH-dependent, and accounting for the protons contributed by the hydroxyls as well as one donated by solvent allowed the authors to assemble the formal binding constants for the multiple borate-vibrioferrin complexes. Extending this analysis to the other two types of siderophores—the catecholates and the hydroxamates—revealed that the former are also competent to bind boron whereas the latter are not. Whether any of these capabilities are in fact used by the siderophore producers is as yet unclear, though low-pH environments may be one place to look. — GJC

J. Am. Chem. Soc. **129**, 10.1021/ja073788v (2007).

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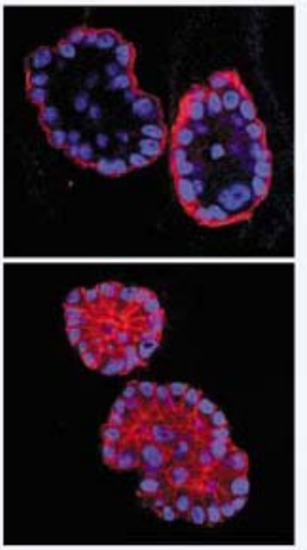
<< Preventing Transformation

The oncogene c-*Myc*, which encodes a transcription factor, is well known for its ability to transform cells. However, not all cells are equally sensitive to c-Myc–induced transformation. Partanen *et al.* compared the responses of organized epithelial acini and of disorganized or immature acini formed from mammary epithelial cells to the transforming ability of a form of c-Myc ($MycER^{tm}$) activated by cell exposure to tamoxifen. When epithelial cells were plated in Matrigel (a three-dimensional cell culture environment prepared from an extract of extracellular matrix) and $MycER^{tm}$ was activated right away, the cells formed misshapen acini and some cells could be seen in the luminal space. On the other hand, cells grown in the absence of activated c-Myc formed symmetrical acini with an empty lumen, and the acini were smaller. If tamoxifen was added after the cells had already formed organized acinar structures, then c-Myc lost its oncogenic activity: The morphology and size of the acini were unchanged, and cell proliferation was not induced. Cells in which the kinase LKB1 (implicated in the establishment of cellular polarity) was silenced formed disorganized acini with disrupted cell polarity when cultured in Matrigel. However, these LKB1-deficient cells did become quiescent. Activation of c-Myc in the LKB1-deficient cells stimulated reentry into the cell cycle, thus confirming the potency of epithelial organization as a brake for oncogenic transformation. The authors also addressed the apoptotic activity of c-Myc, which sensitized cells of fully organized acini to TRAIL (a death-inducing agent that activates apoptosis) and revealed that both TRAIL and Myc were required to promote apoptosis. However, in LKB1-deficient cells with disorganized acini or immature acini, the activation of $MycER^{tm}$ or TRAIL caused apoptosis, and these two agents had an additive effect on cell death. Thus, disorganized epithelia are more sensitive to both the cell-proliferative and apoptotic effects of c-Myc. — NRG

Proc. Natl. Acad. Sci. U.S.A. **104**, 14694 (2007).



c-Myc expression does not alter basal polarity (upper) or cell-cell junctions (lower) in organized acinar cultures.

CREDIT: PARTANEN *ET AL., PROC. NATL. ACAD. SCI. U.S.A.* **104**, 14694 (2007)

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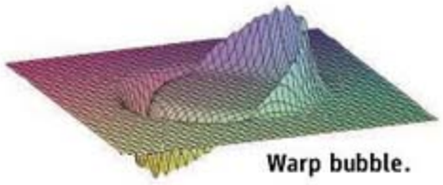
Don't Be Late!

If you're itching to visit other stars, better zip over to London first. On 15 November, the British Interplanetary Society (BIS) will host a workshop titled "Warp Drive, Faster Than Light: Breaking the Interstellar Distance Barrier."

"Warp" refers to the fact that space and time can bend, stretch, and shrink. The conference is based on work by theoretical physicist Miguel Alcubierre, now at the National Autonomous University of Mexico in Mexico City, who in 1994 showed that Einstein's general theory of relativity, which equates gravity with the bending of space and time, could allow for faster-than-light propulsion. He noted that because the universe is expanding, two distant galaxies can move apart faster than light without either one's moving that fast relative to the space around it. Run the film backward, and the galaxies rush toward each other. Combining the effects, Alcubierre showed that in theory, one could move a patch of ordinary space superfast by shrinking space in front of it and stretching space behind it to make a "warp bubble."



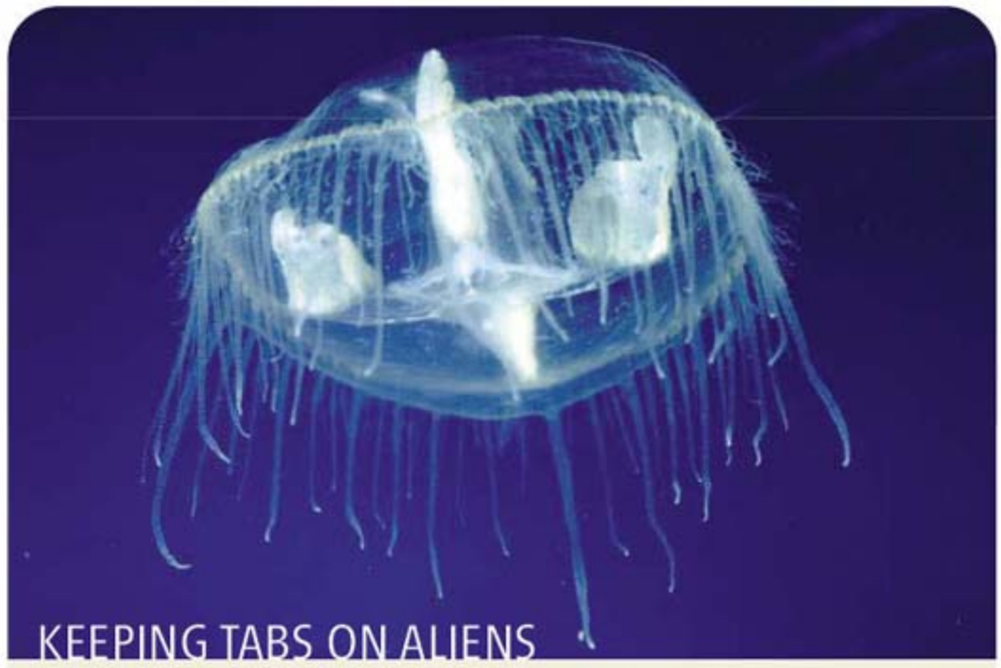
Warp bubble.

There's a hitch, however. The scheme requires "negative energy," which does not exist as far as anyone knows. "The idea was to make a fine point about general relativity, not really to have any practical means of traveling faster than light," says Alcubierre, who will not attend the conference. Physicist Richard Taylor, a consultant to BIS, says it's still "quite exciting to let real scientists talk about things that are almost off-limits."

A Juicy Match

Following up on an intriguing clue from Vietnam, researchers in Florida are studying whether guava trees can control a devastating plant disease called citrus greening. Spread by aphidlike insects called psyllids, the bacterial disease makes fruit taste nasty and then kills trees. It was first spotted in Florida 2 years ago, but citrus growers have yet to figure out how to beat it (*Science*, 28 April 2006, p. 523).

U.S. Department of Agriculture (USDA) researchers recently learned that in Vietnam, orange groves planted with guava trees were disease-free. So they went to look for themselves. "It was pretty much incredible," says entomologist David Hall. "I never found a psyllid in the interplanted fields." The USDA team is now planting some 10,000 guava saplings in test orchards. Hall says it will take at least a year to see if these guava varieties, different from those in Vietnam, ward off psyllids in Florida orange trees, which are not planted as densely as they are in Vietnam. Denise Feiber, a spokesperson for the Florida Department of Agriculture, says she's cautiously optimistic but points out that guava trees attract fruit flies, which could complicate the picture. Ultimately, the scientists say, compounds from guava extracts might be used as sprays.



KEEPING TABS ON ALIENS

NET WATCH

When you think of an invasive species, the freshwater jellyfish *Craspedacusta sowerbyi* (above) probably isn't what comes to mind. But the Chinese native has a firm tentacle-hold in the United States and now lives from coast to coast.

To find out more about this and other aquatic interlopers, visit the NISbase Web site from the Smithsonian Environmental Research Center in Edgewater, Maryland. The site allows you to simultaneously scan nine databases that cover areas as far apart as the Gulf of Mexico, the Mediterranean Sea, and Australia. There are links to images, fact sheets, museum records, and species accounts from the taxonomy hub ITIS. *C. sowerbyi*, you can learn, probably hitched a ride to the United States in ornamental water plants shipped from the Yangtze River valley. >>
www.nisbase.org

Disappearing Tongues

Of 6900 languages spoken in the world today, 6300 are in danger of going extinct, say two linguists who have mapped the world's "language hot spots."

Gregory Anderson and K. David Harrison, a visiting professor at Swarthmore College in Pennsylvania, have taken the concept of "biodiversity hot spots" and applied it to languages, using criteria that include "genetic diversity": the ratio of languages to language families. Bolivia, for example, has as many language lineages as Europe but far fewer languages, which means its language diversity is threatened. Other hot spots are in North America, Siberia, and Australia.

The pair, who are documenting languages with high-tech equipment from the National Geographic Society, have just returned from northern Australia, whose 231 aboriginal languages—from 50 different language families—are almost all endangered. They found a lone speaker of Amurdag, a language that had been thought extinct, and three known speakers each of two other languages, Magati Ke and Yawuru.

"Old Man" Patrick Nanudjul, one of the last three speakers of Magati Ke.

CREDITS (TOP TO BOTTOM): PETER WEISH; ANDREW DEBENEDICTIS/SIMON FRASER UNIVERSITY; K. DAVID HARRISON/2007 / NATIONAL GEOGRAPHIC SOCIETY

EDITED BY YUDHIJIT BHATTACHARJEE

Three Q's >>

The first World Conference on Research Integrity drew 300 people from 52 countries last week to Lisbon, Portugal. *Science* caught up with one of its organizers, **Nicholas Steneck** of the U.S. Office of Research Integrity, which joined with the European Science Foundation to initiate the event.

Q: Did the conference achieve what you wanted?

My expectations changed significantly over time. I had overestimated the level of engagement [on this issue] in many other countries, and therefore we had to back up and do more basic education. From that perspective, I'm enormously pleased.

Q: One speaker called plagiarism a "victimless crime." Were you disappointed by that?

Raising that question is important. I have often said that plagiarism may have a positive outcome … because it still spreads scientific information. … We really do need to assess which behaviors are having the biggest impact on research integrity.

Q: Norway has established a very formal scientific misconduct system with an appointed judge. Do we need a World Court of Research Integrity?

The solutions have to be country-appropriate. What is important is [to] establish minimum standards: There must be a place to report, there has to be reasonable assurance an investigation will take place, [and] there has to be anonymity or at least protection of whistleblowers.

CREDITS (TOP TO BOTTOM): LUÍSA FERREIRA; CAROLE RIFKIND; SOURCE: CHLOÉ LEGRIS

TWO CULTURES

WANT TO TRY IT? After 3 years and 100 hours of tape, Richard Rifkind, chair emeritus of the Sloan-Kettering Institute for cancer research in New York City, is wrapping up a documentary on how science really gets done. *The Lab* chronicles the attempts of graduate student Robert Townley to uncover the atomic structure of AMP-activated protein kinase in Lawrence Shapiro's protein crystallography lab at Columbia University.

Rifkind, a cancer researcher who helped develop the lymphoma drug Zolinza, wanted to portray an important scientific challenge that also would look nice on film in his quest to educate the public about the true process of scientific discovery. Townley didn't pull any punches, either, says Rifkind: "At one point, he looks at the camera and says, 'Two-and-a-half more years of misery.' "

The film is co-produced with Rifkind's wife, Carole, and incorporates a video diary that Townley had been independently keeping for several years. The Rifkinds are in talks with several broadcasters for release rights. The couple's first film, released in 2005, documented the effects of tourism on Venice.

Got a tip for this page? E-mail people@aaas.org

THEY SAID IT

"I propose the following character sequence for joke markers: :-) Read it sideways."

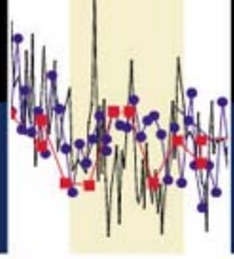
—Scott Fahlman, inventing the first emoticon in a message he posted on an electronic bulletin board 25 years ago. Fahlman, a computer scientist at Carnegie Mellon University in Pittsburgh, Pennsylvania, and his colleagues last week started an annual $500 Smiley Award student contest to foster innovation in technology-assisted person-to-person communication.

CAMPAIGNS

LIGHTS OUT. Darkness has fallen over a sliver of eastern Canada, and astronomers are thanking Chloé Legris for it. The 32-year-old engineer at the Mont-Mégantic Observatory in eastern Quebec province took the lead in persuading federal, provincial, and municipal governments to limit light pollution of the night skies around the observatory. Her efforts led to the first reserve recognized by the International Dark-Sky Association. All of the sky-polluting light fixtures within 25 kilometers of the observatory have been replaced with shaded models that do not project light upward, in the first step of a process that will eventually include neighboring Sherbrooke, a city of 150,000 residents.

The measures should reduce light pollution to the levels last seen 30 years ago, says Robert Lamontagne, director of the observatory. The increased level of light pollution, he says, had "shrunk" the observatory's 1.6-meter telescope to the point at which "there was some research we couldn't do anymore." Legris says public officials saw the light after she explained that replacing 2500 light fixtures with astro-friendly designs would also save 1.3 gigawatt-hours of energy each year.

What a magnetic field does to the brain 1846



How the ice age ended 1847

Double whammy. Northern Nigeria is battling wild and vaccine-derived poliovirus.

INFECTIOUS DISEASE

Vaccine-Related Polio Outbreak In Nigeria Raises Concerns

Northern Nigeria has been hit by one of the largest known outbreaks of poliomyelitis caused by the live polio vaccine itself. The ongoing outbreak could be a serious setback for the global polio eradication campaign: It is occurring in a region where rumors about vaccine safety derailed vaccination efforts several years ago.

Experts with the Global Polio Eradication Initiative emphasize that the widely used trivalent oral polio vaccine (OPV) is safe. But the low immunization rates in northern Nigeria have created the conditions for the attenuated vaccine virus to regain its virulence and trigger an outbreak.

Detected in September 2006, the outbreak of vaccine-derived poliovirus (VDPV) type 2 was immediately reported to the World Health Organization and Nigerian health officials. But the information is just now being released publicly—in the 28 September *Morbidity and Mortality Weekly Report* and WHO's *Weekly Epidemiological Record*—a delay that has caused some consternation in the polio community. Officials say they were worried that the news, if misconstrued, could again disrupt polio vaccination efforts in Nigeria.

"There were legitimate concerns that anti–polio vaccination rumors would be rekindled by an incomplete explanation of the cause of the VDPV outbreak," says Olen Kew, who has led efforts to analyze the outbreak from the U.S. Centers for Disease Control and Prevention in Atlanta, Georgia.

Several polio experts told *Science* that although they understand how sensitive the situation is, they disagree with the decision to keep quiet. "I am troubled that the information hasn't come out, absolutely," says Donald A. Henderson of the University of Pittsburgh Center for Biosecurity in Baltimore, Maryland. Henderson says details of each outbreak are essential if scientists are to understand just how risky these vaccine-derived strains are.

So far, there are 69 confirmed cases of paralysis, and more suspected, caused by VDPV in nine northern Nigeria states, says Kew. The case count seems certain to rise. About half the cases have occurred around Kano, a largely Muslim state where anti-Western sentiment and rumors that the vaccine caused sterility or AIDS led several states to halt polio vaccination in 2003. After repeated demonstrations of the vaccine's safety and considerable behind-the-scenes diplomacy, vaccinations resumed about a year later, but the damage had already been done.

By the end of 2004, the number of polio cases in Nigeria had doubled to about 800, and in 2006 it soared to more than 1100. Wild virus from Nigeria reinfected some 20 other countries, leading to a spike in global cases. It was a huge setback to the Global Polio Eradication Initiative, which estimates that the world spent an additional $500 million to contain the damage. Only recently have global cases dropped back to near preboycott levels.

Although Nigeria has since made considerable progress, wild poliovirus, both type 1 and type 3, is still circulating in the north, and vaccine coverage there remains low. In 2006, between 6% and 30% of children in the north had never received a single dose of OPV.

Those are exactly the conditions that render an area susceptible to outbreaks of vaccine-derived virus. Since the 1960s, scientists have known that attenuated viruses can in rare instances mutate and regain virulence, but it was only in 2000, with an outbreak in Hispaniola, that they realized VDPVs could spread disease from person to person.

The current outbreak came to light when a technician at the CDC polio lab noticed a preponderance of type 2 virus in the isolates sent in from northern Nigeria. That instantly raised suspicion, Kew says, because wild type 2 poliovirus has been eradicated globally. That meant the only possible source was the trivalent vaccine, which had been used in Nigeria in preboycott campaigns. Since Nigeria resumed vaccinations in 2004, says Kew, it had "quite properly" been using the more effective monovalent vaccines against wild types 1 and 3 in its campaigns. Genetic analysis quickly confirmed the source; it also suggests that several VDPVs emerged independently in 2005 and 2006, multiple times.

In earlier outbreaks, circulating VDPVs have been relatively easy to stamp out, but this one has persisted despite four campaigns with trivalent OPV in the past year. "We suspect it is simply because the coverage was not adequate; we don't believe there is anything exceptional about this virus," says Kew. As evidence, he notes that two VDPV strains jumped from Nigeria to Niger, where routine vaccination is almost 90%. Both "barely made it 5 kilometers before they dead-ended," he says.

Polio expert Oyewale Tomori, vice chancellor of Redeemer's University near Lagos and chair of Nigeria's expert advisory committee for polio eradication, says he has been urging officials to go public. He worries that secrecy might fuel suspicions about vaccine safety instead of reinforcing the need to intensify immunizations in Nigeria. **–LESLIE ROBERTS**

CREDIT: JEAN-MARC GIBOUX

Cosmology without a control
1848

The science of forest fires
1854

ENVIRONMENTAL POLICY

Tougher Ozone Accord Also Addresses Global Warming

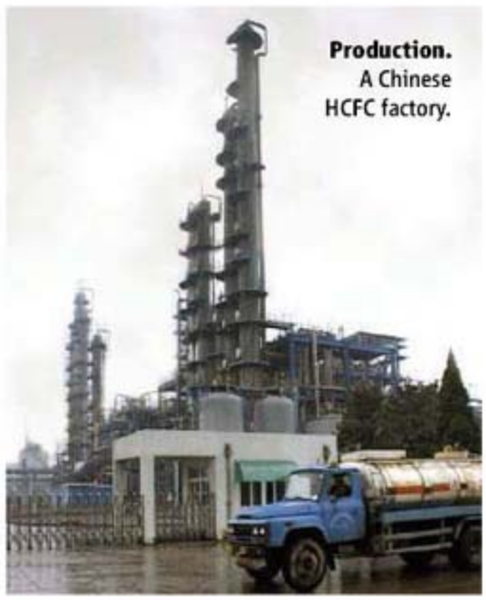
Come for the ozone layer, stay for the climate. That come-on might have been the marketing spiel for negotiators meeting last week under the aegis of the United Nations Environment Programme to strengthen the Montreal Protocol, the 20-year-old accord on chlorofluorocarbons (CFCs) and other chemicals that deplete the ozone layer. And it worked. The delegates who returned to the city from which the 1987 treaty got its name also made significant progress in combating global warming by recognizing the fact that most chemicals affected by the treaty are also potent greenhouse gases and that restricting them pays double dividends.

The thin shell in the stratosphere that protects Earth from the sun's rays has a variety of enemies, and the Montreal Protocol has been tightened four times as scientists have placed restrictions on newly recognized threats. As a result, the rate of harmful emissions has slowed (see graph), and more than 90% of the production and use of ozone-depleting chemicals has been phased out. The biggest threats may have passed, say experts, but this year's weeklong meeting set itself two main goals: to clamp down on ozone-harming refrigerants that have become prevalent in the developing world, and to do it in a way that could provide tangible side benefits for climate.

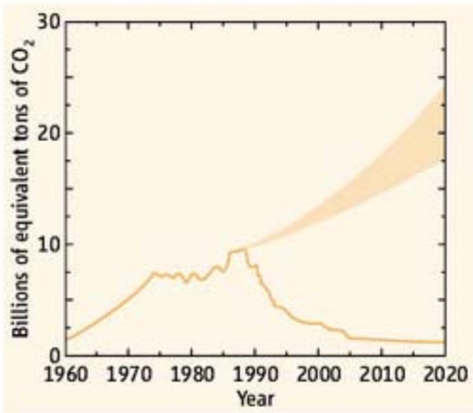
By the end of the meeting, they could claim to have met both goals. Most impressive was an agreement by delegates to push forward by a decade a legally binding schedule to phase out in developing nations a family of chemicals called hydrochlorofluorocarbons (HCFCs). The 191 participating nations also pledged to finance a transition fund, currently funded at roughly $150 million per year, to support the conversion to alternatives. And with the urging of U.S. officials, the delegates also pledged to make sure that the HCFC replacements would have the lowest possible harmful impact on global warming.

"The delegates deserve lots of credit for both recognizing and seizing a historic opportunity to protect both the ozone layer and the climate," says Alexander von Bismarck of the Environmental Investigation Agency, a London-based nonprofit that has monitored the treaty. Activists hope the action gives momentum to international meetings on climate change occurring in New York and Washington, D.C., as *Science* went to press.

The Montreal Protocol arose out of two scientific developments. In 1974, chemists F. Sherwood Rowland and Mario Molina calculated that CFCs, a common ingredient in spray cans, could destroy stratospheric ozone. Although that discovery led to some voluntary curbs on their use, the impetus for mandatory action came in 1985, when British scientists measured an ozone "hole" over the Antarctic. The new agreement is consistent with the findings of a scientific assessment in August that said an accelerated HCFC phaseout in developing countries would produce the equivalent savings of 18 billion tons of carbon dioxide emissions by 2050. HCFCs were meant to be a transition chemical as countries phased out CFCs, but they have been widely used as coolants in the booming economies of China and India.



Production. A Chinese HCFC factory.



Protection. The 1987 ozone treaty has reduced global greenhouse gas emissions that otherwise would have risen sharply.

The agreement would freeze HCFC production by developing nations in 2013—2 years earlier than planned—followed by successive cuts until production was ended in 2030, a decade sooner than previously agreed. Developed nations agreed to advance their deadline for a phaseout from 2030 to 2020, as well as promising to provide "stable and sufficient" funds for replacements while "taking into account global warming potential" in deciding which chemicals to accept as substitutes.

"You couldn't have imagined this 5 years ago," says Durwood Zaelke of the nonprofit Institute for Governance and Sustainable Development (IGSD) in Washington, D.C. The current availability in China of products with many of the HCFC alternatives bodes well for the new agreement, says DuPont chemist Mack McFarland. An important driver during talks was a statement from the G8 summit in June, pushed by the U.S., pledging the industrial powers to climate-friendly action on ozone. "It's being held up [as an inspiration] by all the parties" during negotiations, said IGSD's Scott Stone, who attended last week's conference. "This [showed] great leadership by the White House."

The reviews weren't entirely positive. Delegates agreed to U.S. demands to continue an exemption for ozone-unfriendly methyl bromide, a fumigant used by U.S. farmers, allowing annual emissions of 4600 tons. David Doniger of the Washington, D.C.–based Natural Resources Defense Council, which wants a full phaseout, called that "a black mark" on an otherwise strong U.S. performance. White House environment aide James Connaughton says U.S. negotiators hope to build on the success in Montreal during a 2-day meeting hosted by the Bush Administration this week attended by representatives from 15 industrial nations and major emitters. **–ELI KINTISCH**

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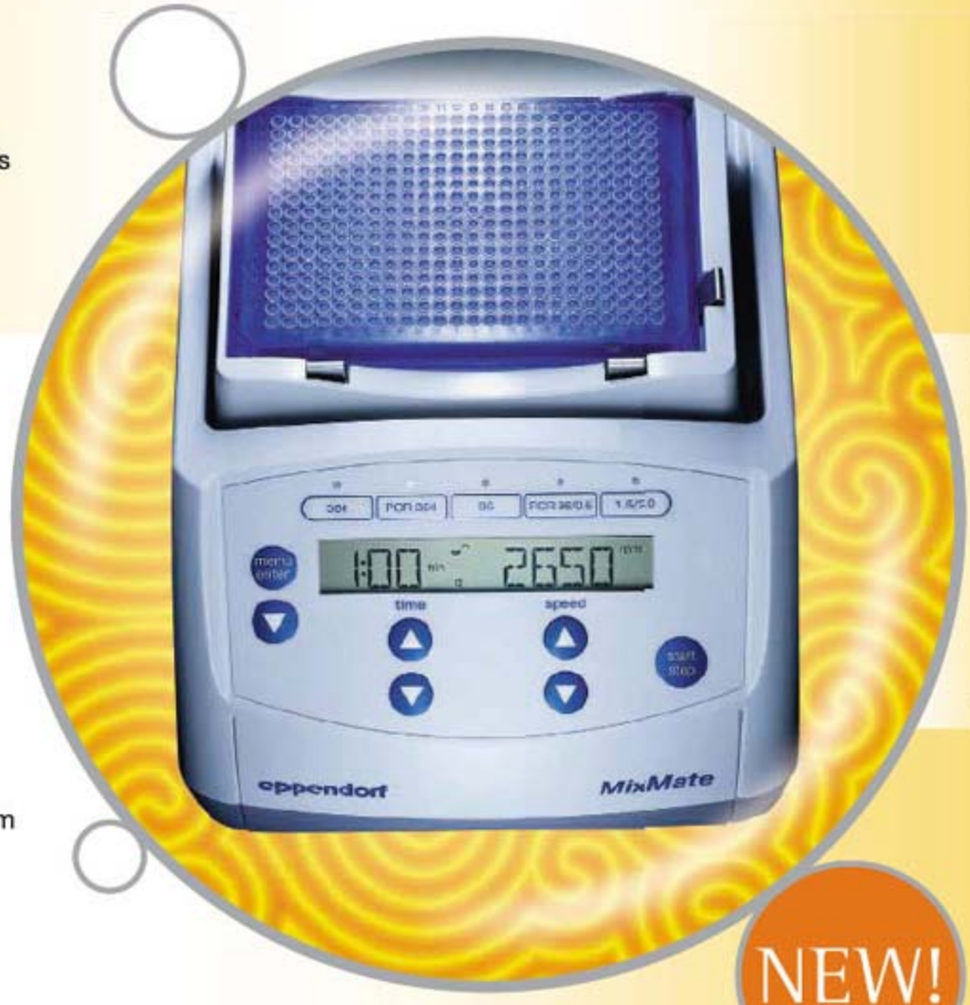

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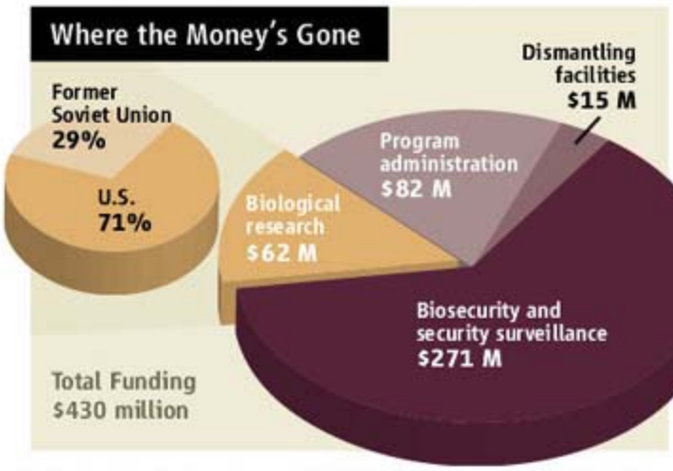
BIOWEAPONS

Panel Wants U.S. Program to Retain Its Russian Roots

Four years ago, scientists in Obolensk, Russia, wanted to ship a strain of anthrax to a lab in Fort Detrick, Maryland, under a U.S. program intended to prevent former bioweapons scientists from selling their expertise to terrorists or "rogue" nations. But the Russian government wouldn't give the Obolensk lab an export license.

Such setbacks are one reason the Department of Defense (DOD) has decided to phase out collaborative research projects in Russia under its Biological Threat Reduction Program. But a new report by the U.S. National Academies' National Research Council (NRC) says the agency is making a mistake. It calls on DOD to increase support for the program and to give Russian administrators and scientists a greater voice in determining its direction.



Whose threat? U.S. entities have received most of the money for research on reducing the threat of Russian bioweapons.

SOURCE: DEFENSE THREAT REDUCTION AGENCY

Since 1998, the agency has spent more than $430 million on dismantling biological weapons production centers, improving security at research facilities, setting up disease surveillance networks, and supporting scientists throughout the region. The activities are part of the U.S. government's biological nonproliferation efforts in the former Soviet Union. DOD officials plan to continue, and even increase, support for scientists in other countries in the region. But the difficulties in gaining access to Russian labs, combined with an improved outlook for funding science that stems from the country's robust economy, have made Russia the odd man out. "We think the Russians are now perfectly capable of transitioning their former weapons labs to make them part of their public health system," a senior DOD official told *Science* this summer.

The academies report, requested by DOD's Defense Threat Reduction Agency (DTRA) at the urging of Congress, takes a different view. "Although the economic situation in Russia is stabilizing, the future of a large number of biological institutions is in flux," it says. "And many former weapons scientists remain trapped in uncertain circumstances that could raise serious proliferation concerns." The bottom line, according to NRC's Glenn Schweitzer, is that "Russia is too important a country to not engage in."

The report cites the program's success in improving security at a number of Russian labs. And it suggests that heeding the wishes of its Russian hosts would strengthen the program. "DOD continues to be interested only in studying pathogens it considers dangerous for bioterrorism, while the Russians want to tackle health problems like cholera and tuberculosis," explains Sonia Ben Ouagrham-Gormley of the Monterey Institute of International Studies in Washington, D.C. The fact that most of the money has gone to U.S. contractors and visiting scientists has also soured Russians on the program, the report notes.

The panel's recommendations are right on the mark, says Carleton Phillips II, a biologist at Texas Tech University in Lubbock and the principal investigator on a DOD-funded project in Kyrgyzstan aimed at mapping the distribution of mammals that are reservoirs of infectious diseases. He says the best way to reduce biological threats in the former Soviet Union is to "engage local scientists in true collaborations."

Now that the experts have spoken, will DOD listen? A DTRA official says the report "will definitely have an impact on the future of the program," adding that the agency plans to respond before the end of the year. A staffer on the Senate Foreign Relations Committee also likes the report's recommendations. "There is basic support on the Hill for doing more collaborative research in Russia," he says.

–YUDHIJIT BHATTACHARJEE

Dam Californians

California Governor Arnold Schwarzenegger has fired the latest shot in the state's perennial battle over water. He's proposed a $9 billion bond measure to increase the state's water supplies by, among other steps, building two new dams in the north of the state and channeling water through or around the Sacramento–San Joaquin River delta. The environmentally sensitive delta is beset by crashing fisheries, pollution, and invasive species (*Science*, 27 July, p. 442).

Schwarzenegger says the new water infrastructure is part of a "comprehensive fix." But opponents say water conservation is a better solution. Science should help sort out the options, says Peter Moyle, a fisheries biologist at the University of California, Davis: "There's a lot we don't understand [about] how these plans will affect fish." –ROBERT F. SERVICE

Pounds for Paws

Britain's largest medical research charity hopes to help veterinarians keep up with the latest developments with a $22.5 million initiative to recruit them into research. In 2004, the U.K. government provided $43 million to boost the number of scientists trained to tackle challenges such as foot-and-mouth disease. But that program ends in 2009. Last week, the Wellcome Trust made awards to seven U.K. veterinary schools for efforts including summer courses and postdoctoral training. "This is an absolutely vital development," says Christopher Stokes of the University of Bristol, one of the recipient universities. –ELIE DOLGIN

White House: Risk-Averse

After getting slammed by the National Academies' National Research Council (NRC), the White House Office of Management and Budget (OMB) has decided not to issue a controversial directive on risk assessment. The draft bulletin, released in January 2006, contained guidelines and technical standards on issues such as expressing uncertainties in federal risk assessments. But a subsequent NRC report requested by OMB called the approach "fundamentally flawed," saying, for example, that it would require uncertainty analysis "beyond the current state of the science" (*Science*, 19 January, p. 316). In reversing the move, OMB has instructed agencies to follow "generally accepted principles for risk analysis" issued by the Clinton Administration. That's "good news for the science community," says Rick Melberth of the advocacy group OMB Watch in Washington, D.C. –ERIK STOKSTAD

NEUROSCIENCE

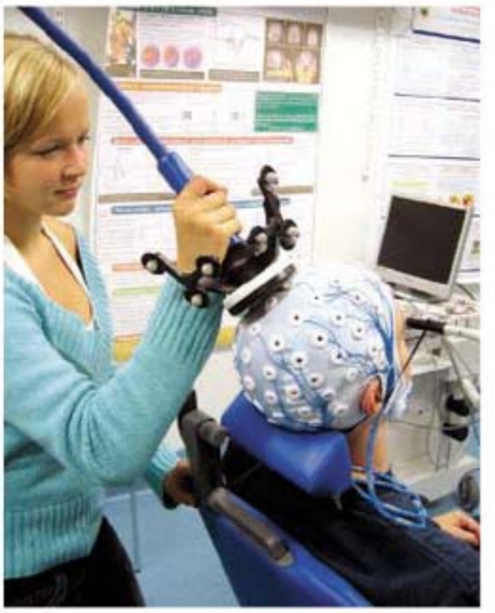
Uncovering the Magic in Magnetic Brain Stimulation

In recent years, neuroscientists and psychiatrists alike have touted the potential uses of a noninvasive brain stimulation technique called transcranial magnetic stimulation (TMS). The method has been used to disrupt neural activity experimentally in studies of human cognition, and it has shown promise in clinical trials for treating psychiatric disorders such as depression (*Science*, 18 May 2001, p. 1284). Although widely considered safe—thousands of people have received TMS—relatively little is known about how it actually works. Now, a detailed look at its effects shows that TMS can boost or dampen the firing of neurons depending on ongoing brain activity.

Neuroscientists at the University of California, Berkeley, applied TMS to the cerebral cortex of cats while monitoring neural activity and metabolism. Their findings, reported on page 1918—and future investigations of this type—will have important implications for how TMS is used in people, other researchers say.

One interesting possibility, according to Mark George, a psychiatrist at the Medical University of South Carolina in Charleston, is that it may matter what subjects think about while they're being stimulated, a factor that hasn't received much consideration to date. George, who pioneered TMS therapy for depression, says a better understanding of how TMS works will enable researchers and clinicians to apply it more effectively: "This is precisely where the field needs to go."

In a typical TMS procedure, technicians place a ring-shaped paddle near the scalp. Electric currents swirling inside the paddle produce a magnetic field that in turn generates currents in the underlying brain tissue. These currents alter the electrical activity of neurons, but exactly how they alter it is poorly understood.



Stimulating results. New research hints at the mechanisms of magnetic brain stimulation.

Led by Ralph Freeman and graduate students Elena Allen and Brian Pasley, the Berkeley scientists applied TMS to the visual cortex of anesthetized cats and tracked the aftermath using probes developed in Freeman's lab that can simultaneously record the electrical activity of neurons and measure fluctuations in oxygen concentration, an indicator of energy consumption. Using optical imaging methods, the researchers also tracked hemoglobin levels, another metabolic marker. A train of TMS pulses lasting a few seconds caused an immediate increase in neural firing that lasted for about a minute, followed by a decrease in firing for several minutes. Oxygen and hemoglobin mirrored this pattern, indicating that neurons' firing and energy demands go hand in hand.

TMS had a dramatically different effect, however, on neural activity evoked by black and white bars flashed on a computer screen. (Such responses persist even in anesthetized animals.) In this case, neural firing dipped sharply after TMS and remained suppressed for several minutes.

The findings have implications for designing TMS therapies, says George. For depression therapy, for example, "we may need people to become sad in the chair while stimulating [them]," George says. "Alternatively, we might have them engage in formal cognitive therapy, thinking positive thoughts." Such considerations are important, he adds, as the Food and Drug Administration is considering approval for daily TMS of the prefrontal cortex to treat depression.

The new findings also suggest why the effects of TMS often vary, says Alvaro Pascual-Leone, a neurologist at Harvard Medical School in Boston. Pascual-Leone suggests that TMS results could be made more consistent by monitoring the physiological state of the brain using electroencephalography or functional magnetic resonance imaging. **–GREG MILLER**

CREDIT: COURTESY OF HANNA MÄKI/LABORATORY OF BIOMEDICAL ENGINEERING, HELSINKI UNIVERSITY OF TECHNOLOGY AND BIOMAG LABORATORY, HELSINKI UNIVERSITY HOSPITAL

ENGINEERING

Pollution Slows China's Canal Project

The first phase of a massive project to replumb some of China's mightiest waterways has fallen far behind schedule because local authorities don't want to pay for the privilege of drinking polluted water.

The South-to-North Water Diversion Project is a three-stage effort to alleviate chronic water shortages in the country's more populous but parched northern plains (*Science*, 25 August 2006, p. 1034). The eastern route makes use of an existing network of canals, rivers, and lakes to pump and move water from the lower Yangtze River to Jiangsu and Shandong provinces. But this month, the official Xinhua news agency announced that the first phase of the route, scheduled to begin operating this year, has been delayed at least 3 years.

Nearly half of the $4 billion cost of the first phase is earmarked for improving the quality of the water. However, the central government is footing only about 10% of the bill, with the rest expected to come from localities that will benefit from the project. But because nobody wants to clean up somebody else's dirty water, few treatment facilities have been built along the route, and water quality continues to deteriorate. So far this year, according to Xinhua, the water is drinkable at only one of the 21 monitored cross sections in Shandong.

Some engineering experts say the entire project itself needs to be rethought, with a greater emphasis placed on improving the ecology of the Yellow and Huai river basins. Dredging the Grand Canal north of the Yellow River to make the ancient waterway navigable, they say, would provide a greater benefit to the region and, thus, attract more investment.

Qian Ye, a climate researcher at the U.S. National Center for Atmospheric Research in Boulder, Colorado, thinks the Chinese government should do a more comprehensive feasibility study of the project that considers the impact of climate change. Global warming, he says, could make China's north wetter and allow authorities to scale back the controversial project. **–HAO XIN**

Long story. A lengthy sediment core tells of an early thaw.

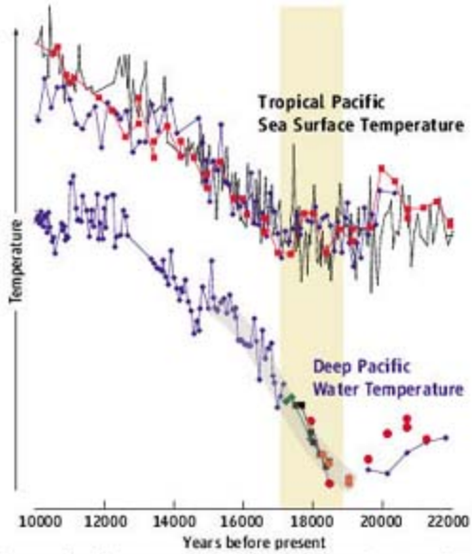
CLIMATE CHANGE

A Far-South Start for Ice Age's End

Where was the thermostat switch that, once thrown, began to thaw the world out of the last ice age? Paleoceanographers long assumed that it lay in the North Atlantic Ocean somewhere; then the tropical ocean gained popularity in some quarters. But now, strong new evidence from the tropics places the start yet farther south, in the waters around Antarctica. The result "is all very solid, very hard to question," says paleoceanographer William Ruddiman, professor emeritus at the University of Virginia, Charlottesville. "But it also tells us things are complicated. There are just layers of complexity to this."

Finding where it all started "comes down to timing," says paleoceanographer Lowell Stott of the University of Southern California in Los Angeles. But determining the timing of climate events can be tough when, say, warming in the tropics is recorded in marine sediment, whereas warming in Antarctica is recorded in glacial ice. Those are dated by entirely different methods, which injects an uncomfortable amount of uncertainty.

Stott and colleagues Axel Timmermann, a modeler at the University of Hawaii, Manoa, and paleoceanographer Robert Thunell of the University of South Carolina, Columbia, eliminated that uncertainty, at least, by gauging changing temperature in western Pacific surface waters and in Antarctic waters in a single sediment core recovered just west of the Philippine island of Mindanao. At any point in the core, microfossils that had fallen from western Pacific surface waters recorded temperature there in their oxygen isotopic composition, whereas microfossils that always lived on the sea floor recorded the temperature of bottom water that had sunk from the surface of the Southern Ocean near Antarctica. Then the group radiocarbon-dated the sediment.



CREDITS: (PHOTO) L. D. STOTT/UNIVERSITY OF SOUTHERN CALIFORNIA; (GRAPHIC) ADAPTED FROM L. D. STOTT *ET AL.*, SCIENCE

A southerly start. Water from near Antarctica (*bottom*) warmed before the tropics (*top*).

The results, reported online at www.sciencemag.org/cgi/content/abstract/1143791, were startling. In an earlier *Science* paper, Thunell and Stott had concluded that the tropical Pacific had warmed first, presumably causing glacial ice to begin melting. But their new analysis shows that more than 18,000 years ago, Antarctic waters warmed 1000 to 1300 years before tropical waters.

Starting from that timing and drawing on other dated records, Stott and colleagues spin a tale of how the ice started melting. First, predictable variations in Earth's orbit and tilt increased the amount of sunlight hitting high southern latitudes during austral spring. That warmed things up locally and shrank the sea ice back toward Antarctica, uncapping the Southern Ocean and freeing much of its carbon dioxide to begin warming the whole world.

Nice story, other researchers say, and the starting point at least seems fairly solid. "I think they make a convincing case that something is happening at high southern latitudes before tropical temperatures change," says paleoceanographer Jean Lynch-Stieglitz of Georgia Institute of Technology in Atlanta. But, as she and Ruddiman both note, putting together the deglaciation story is "a tricky business." And there are dissenting voices. Paleoceanographer David Lea of the University of California, Santa Barbara, says it isn't so clear polar warming preceded tropical warming, given the difficulty of picking out exactly when the tropical warming began. All agree that finishing up the story in the Northern Hemisphere—where most ice melting eventually occurred—will take much more work. **–RICHARD A. KERR**

SCIENCESCOPE

Bank Withdrawal

Both U.S. senators from New York—Hillary Clinton (D) and Charles Schumer (D)—are demanding that the U.S. Department of Veterans Affairs (VA) create a gene bank at the University at Albany in New York state. The pair argues that the project was approved but that the VA never followed through. The idea has enormous potential: More than 7 million veterans could donate DNA. But for now it is tangled in controversy. After inking an agreement with the university nearly 4 years ago, the VA began to pursue a gene bank project on its own, upsetting the Albany group, which is led by cancer biologist Paulette McCormick (*Science*, 29 July 2005, p. 684). Last week Clinton and Schumer took up the case, suggesting in a letter to VA Secretary R. James Nicholson that "the Department may be using the concepts developed by Dr. McCormick to establish a gene bank in another location." They urged the VA to set up a gene bank at SUNY-Albany.

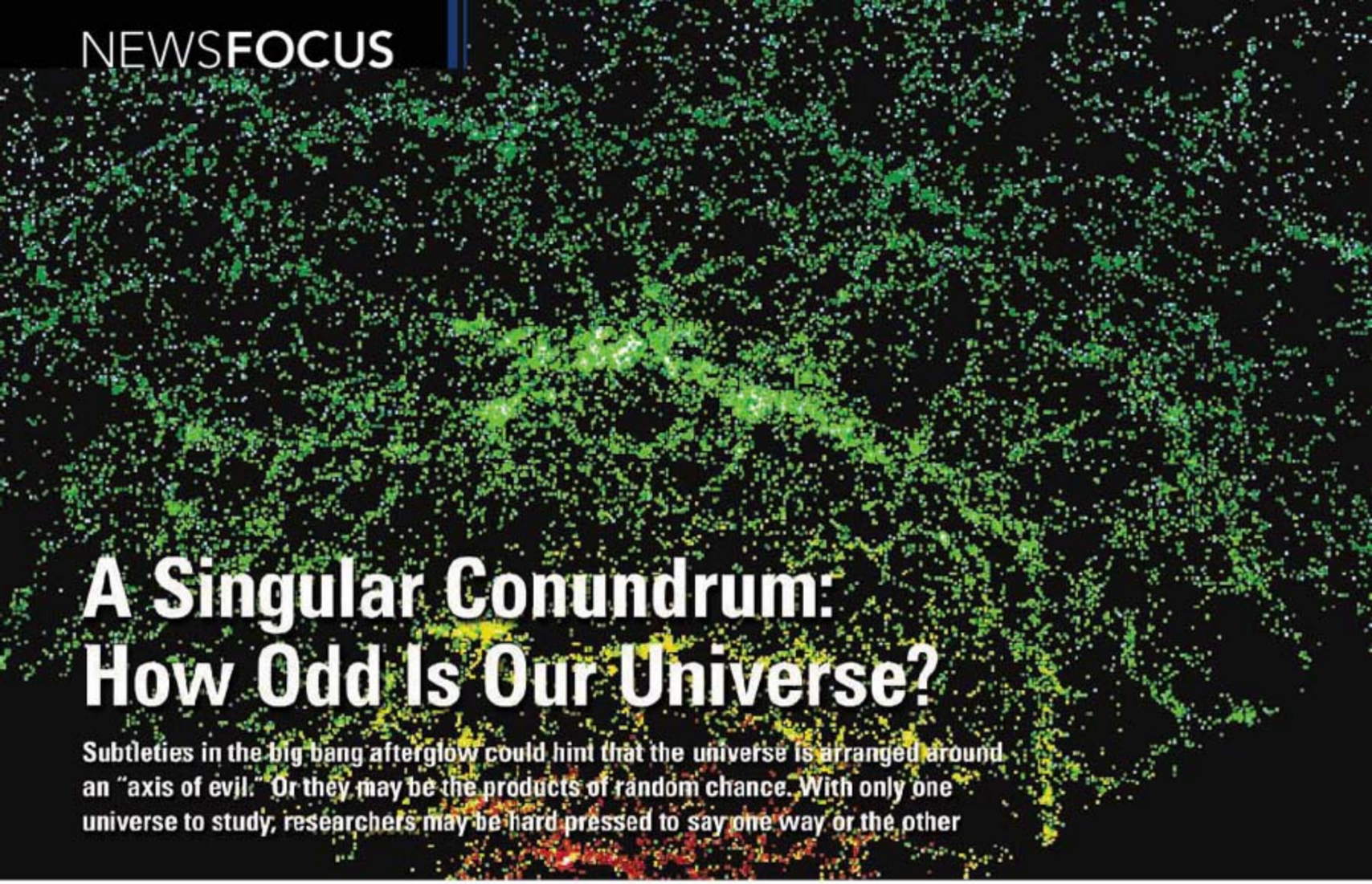
Joel Kupersmith, the VA's chief research and development officer, declined to comment on the dispute. But he says that although VA researchers are only collecting specimens for individual projects now, "our plan in the long run" is to assemble a vast store that could be used by outside investigators.

–JENNIFER COUZIN

NuSTAR Is Reborn

NASA resurrected a mission to study black holes last week and now plans to orbit the spacecraft by 2011. The Nuclear Spectroscopic Telescope Array (NuSTAR) will use high-energy x-rays to image the areas around black holes that congregate at the center of galaxies. The space agency killed the idea in 2006 because of funding constraints. But NASA science chief S. Alan Stern said in a statement that he reversed that decision because "we're getting more and more from the science budget we have, and the restart of the highly valued NuSTAR mission is an example of that." That's music to the ears of the researchers who thought all was lost for a mission originally slated for launch this year. "I'm personally incredibly excited," says Caltech physicist Fiona Harrison, the principal investigator on the project.

Not every project got good news last week. Stern also approved a plan to reduce the number and complexity of instruments on the Mars Science Laboratory because of cost overruns. That is raising howls from Mars exploration advocates. The Pasadena, California–based Planetary Society called the move "penny-wise and pound foolish." **–ANDREW LAWLER**



A Singular Conundrum: How Odd Is Our Universe?

Subtleties in the big bang afterglow could hint that the universe is arranged around an "axis of evil." Or they may be the products of random chance. With only one universe to study, researchers may be hard pressed to say one way or the other

THE UNIVERSE: THERE'S NOTHING ELSE like it. So if the cosmos is strange in some way, how would you tell? That may sound like the beginning of an annoying argument among philosophy majors. But cosmologists have been debating just this point as they try to figure out whether—just maybe—our universe is even weirder than they thought.

The controversy has been simmering for some time. In 2003, NASA's Wilkinson Microwave Anisotropy Probe (WMAP) satellite measured the light lingering from the big bang (*Science*, 14 February 2003, p. 991). Researchers charted the slight variations in the temperature of the radiation, known as the cosmic microwave background (CMB), to produce a sky map resembling a dimply lime. Analyzed statistically, that iconic map bolstered a bizarre scenario called inflation, in which in a billionth of a trillionth of a trillionth of a second, the newborn universe doubled and redoubled in size 100 times over, stretching each atom-sized volume to the size of a galaxy.

But the map led to some mysteries, too. Within 6 months, one team had found a curious alignment of certain undulations in the CMB. Others soon found more correlations that suggested that the cosmos might be skewered like a meatball on a toothpick by an "axis of evil." That axis might show that the universe has a strange shape or is rotating. It could trash cosmologists' cherished assumption that the universe has no center and no special directions, the so-called cosmological principle that traces its origins to Copernicus. Or it could be a meaningless fluke. "Everyone agrees it's there," says Kate Land, a cosmologist at the University of Oxford in the U.K. "But is it significant?"

There's the rub: With only one universe to measure, it may be impossible to tell. Modern cosmological theory mixes the elegant predictability of Einstein's theory of gravity with the inherent randomness of quantum mechanics, which held sway when the universe was just an infinitesimal speck. So theorists can predict the statistical or average properties of the universe, but not the individual quirks and coincidences caused by random quantum fluctuations all those billions of years ago.

> **"If our universe is unusual, what does it mean?"**
>
> —Kate Land, University of Oxford

Moreover, although the universe in toto may be infinite, we see only a finite part of it. Because the universe is expanding and the speed of light is finite, anything beyond 50 billion light-years away is zooming off so fast we'll never glimpse it. So the axis could hint at some fundamental feature of the entire universe. Or it could be a meaningless peculiarity of the bit we can see, our so-called Hubble volume or observable universe. Deciding will be difficult, as it's impossible to peer into neighboring Hubble volumes or to repeat the "experiment" that produced our homey patch of the infinite.

"The main problem with cosmology is our sample size—that of just one universe," Land says. "If our universe is unusual, what does it mean?" The question underscores just how much cosmologists' observations have improved in the past 2 decades. "In the past, our frontier has always been set by technology; you could always build a bigger telescope and look deeper," says Max Tegmark of the Massachusetts Institute of Technology (MIT). "For the first time, we've hit the final frontier."

So far, only measurements of the CMB have run up against that barrier. But as cosmologists launch studies that take all they can see as one measurement, other efforts could hit it, too. A few researchers think that the matter undermines cosmology's status as a

CREDIT: MAX TEGMARK/SDSS

Weirdness ahead? Future maps of all the galaxies will be scrutinized for unexplained patterns.

science. All agree that having only one observable universe means that some of its quirks may remain forever mysterious.

Fanfare for the common universe

Like a Jimi Hendrix power chord, the CMB reverberates through time. The harmonies in the electromagnetic echo reveal the state of the universe when the chord was struck instantly after the big bang.

According to current theory, the universe popped into existence infinitely dense and hot and crammed with light and subatomic particles. Within 10^{-33} seconds, inflation stretched it immensely, before its expansion slowed to a more leisurely pace. Inflation evened out the temperature of the universe, stretched space as flat as a taut bed sheet, and diluted to nothing the numbers of certain pesky particles that theorists say should exist but that have never been seen.

The big blowup also sowed the seeds for the ripples in the CMB. The stretching magnified tiny quantum fluctuations in the soup of fundamental particles, creating slight variations in its density. Matter began to coalesce into the denser spots, setting off a sloshing of light and matter and leading to tiny temperature variations. These are the same variations conveyed by the CMB, which began shining through the cooling universe 400,000 years after the big bang, when light-trapping protons and electrons combined to form transparent hydrogen atoms.

To decipher the mottled CMB map, WMAP researchers broke it down much as a musical chord can be broken into individual pitches. Any spherical map can be viewed as the sum of coarser and finer undulations called harmonics or multipoles. For the CMB, the coarsest, the dipole, simply divides the sky into hotter and colder halves. The next, the quadrupole, divides the sky roughly in four, into the two hottest and two coldest regions, and so on. Researchers measured the strengths of hundreds of harmonics and plotted them in a so-called power spectrum, the cosmological equivalent of musical notation specifying which notes to play louder or softer.

The WMAP team then tried to match this spectrum to the predictions of cosmological theory. They found they could do just that if the universe is precisely 13.7 billion years old and flatter than an Illinois cornfield. It also has to contain 4% ordinary matter; 23% dark matter, which has revealed itself only through its gravity; and 73% space-stretching dark energy, which is currently accelerating the expansion of the universe (*Science*, 19 December 2003, p. 2038).

The power spectrum also rises and dips in several places, revealing how sound waves rippled through the toddler universe. Inflationary theory predicted the nature of the bumps and wiggles, and the WMAP data fit the predictions precisely, says Charles Bennett, a cosmologist at Johns Hopkins University in Baltimore, Maryland, and leader of the WMAP team: "It certainly was a major victory for inflationary cosmology."

> **"Cosmology may look like a science, but it isn't a science"** because it's impossible to do repeatable experiments.
>
> —James Gunn, Princeton University

The axis emerges

Amid the cacophony, however, scientists detected some distinctive harmonies. In 2004, MIT's Tegmark and Angélica de Oliveira-Costa, both then at the University of Pennsylvania, reported in *Physical Review D* that the hot and cold spots of the octopole pattern are arrayed around a single axis a bit like the panels on a basketball. Moreover, this axis appears to line up with a similar axis for the quadrupole. They estimated the chances that the alignment is a fluke at 1 in 66.

A few months later, another team found more curious alignments. The axis defined by the quadrupole and the octopole lies in the plane of the solar system, known as the ecliptic, and points toward the equinoxes, the two points on Earth's orbit at which night and day are equal length all over the planet, reported Glenn Starkman of Case Western Reserve University in Cleveland, Ohio, Dominik Schwarz of the University of Bielefeld in Germany, and colleagues in *Physical Review Letters*.

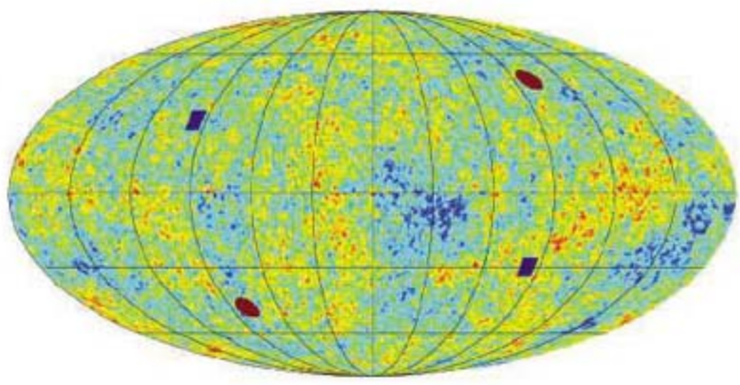
Then, in 2005, Oxford's Land and João Magueijo of Imperial College London reported that the next two harmonics also appear to be aligned with the quadrupole and octopole. They interpreted that as possible evidence that the universe is in fact arrayed around a special axis. If that were true, the cosmological principle would go out the window. The alignments are all the more suggestive because they involve the broadest undulations on the microwave sky, Land says: "If there were something odd cosmologically, this is where you'd expect it to kick in."

Many are skeptical. "If you look at a data set in 1000 different ways, you expect to find something that's unusual at the 1-in-1000 level," WMAP leader Bennett says. Some suspect that the axis may be an illusion produced by an unaccounted bias in how the satellite works. And even those who have studied the alignments note that exactly how unlikely they appear depends on which mathematical tools researchers use to analyze them. Still, many are taking it seriously. "I would say that with a bit more than 99% confidence you can say there's something strange," Schwarz says.

Axis-stential musings

Assuming the axis is more than a measurement error, what new physics might it point to? The most conservative explanation is that the alignments reflect contamination from some nearby stuff that either emits or absorbs microwaves. Researchers already have to filter out the "foreground" microwave glare from the disk of the galaxy. A signal originating within the solar system might explain the connection to the ecliptic—although that would be far more likely if the axis ran parallel to the axis of the solar system, not perpendicular to it.

Such a foreground would be sexier than it sounds at first, Starkman says. At the least, it would reveal new astrophysics, perhaps some really bizarre form of dust. Moreover, the presence of a foreground from the solar system would most likely only bolster the case for the cosmic axis, he says. Strange though it may sound, compensating for such a foreground would probably accentuate the oddities. "The chances are that when you subtract it, the data will agree even less well with the theory than



CREDIT: NASA/WMAP SCIENCE TEAM

Poles apart. The axis of evil (poles marked red) lies almost perpendicular to the solar system's axis (poles marked blue) and far from the galactic axis.

they do now," Starkman says.

By far the most exciting possibility is that the axis indicates that the universe is stranger than cosmologists have assumed. For example, the universe could whip up such an axis if space had an odd shape, such as a torus that wraps around and reconnects to itself. "If you want to explain the axis of evil, the easiest way would be to say that our universe is a lot like [the video game] Asteroids, where if you go off the screen on one side, you come back on the other," Tegmark says. Others have proposed weirder shapes or suggested that the whole universe could be spinning around the axis.

None of these tantalizing ideas has bowled researchers over, however. Tegmark and de Oliveira-Costa's doughnut universe clashes with other observational constraints. If the universe wraps around in such a way, then researchers should see faint matching circles in the CMB on opposite sides of the sky (*Science*, 22 June 2001, p. 2237). But none have been found. Other models suffer similar problems. "It's tough because on one hand, I'm on the side of saying that this may be telling us something," Starkman says. "On the other hand, so far I'm unconvinced by the ideas that have been put forward for what this might be telling us."

Of course, the axis could just be a fluke, a coincidence produced by primordial quantum fluctuations in our particular Hubble volume. Although Albert Einstein insisted that "God does not play dice"—so often that others tired of hearing it—theorists now think that in making the cosmos, the metaphorical creator rolled the bones once and walked away. Perhaps, like troubled gamblers, some cosmologists read too much into the fact that he tossed a 2 and a 3.

One thing is certain: Cosmologists will never figure out what the axis of evil is by remeasuring the CMB. Researchers have measured the temperature variations in the CMB so precisely that the biggest uncertainty now stems from the fact that we see the microwave sky for only one Hubble volume, an uncertainty called cosmic variance. "We've done the measurement," Bennett says. "It's not going to get any better."

The geology of the cosmos

To be sure, many things remain to be measured. But cosmic variance could ultimately pinch other sorts of studies, such as galaxy surveys. Researchers with the Sloan Digital Sky Survey are using a 2.5-meter telescope at Apache Pointe, New Mexico, to map everything they can see in a quarter of the sky and have spotted 80 million galaxies so far. The proposed 8.4-meter Large Synoptic Survey Telescope (LSST) aims to tally 3 billion. By the middle of the century, researchers likely will have surveyed all 100 billion bright galaxies in our Hubble volume, says Michael Turner, a cosmologist at the University of Chicago in Illinois.

> **"The fact that we can only see one Hubble volume has not been an impediment** to understanding the origin and evolution of the universe."
>
> —Michael Turner, University of Chicago

Such surveys aim to study the distribution of the galaxies en masse, or how the galaxies' images are distorted by huge threads of dark matter spanning the universe. In doing so, they trace the evolution of the density fluctuations that rippled the CMB. That's because those fluctuations also spawned the dark matter filaments, which in turn seeded the galaxies. Even with LSST, some of those studies will butt against the limits of cosmic variance, says Lloyd Knox of the University of California, Davis.

That barrier to knowledge, some argue, is cosmology's Achilles' heel. "Cosmology may look like a science, but it isn't a science," says James Gunn of Princeton University, co-founder of the Sloan survey. "A basic tenet of science is that you can do repeatable experiments, and you can't do that in cosmology." Others don't see the problem. "So far, the fact that we can only see one Hubble volume has not been an impediment to understanding the origin and evolution of the universe," Turner says. Some note that cosmic variance will limit measurement of only the very largest features of the universe and that studying the myriad smaller bumps and wiggles may be more revealing anyway.

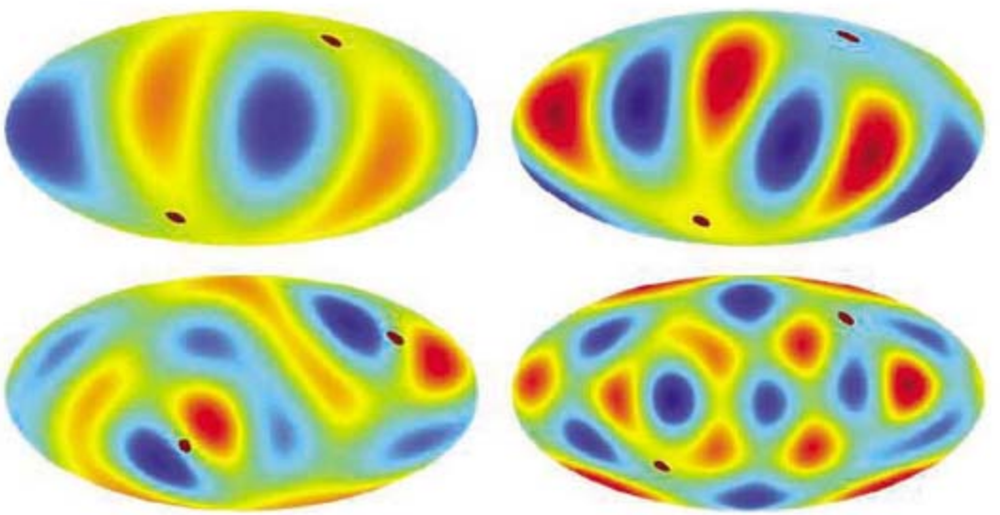
Even so, all agree that cosmic variance highlights a definite limit to what cosmology can tell us. "The goal of physics is to understand the basic dynamics of the universe," Turner says. "Cosmology is a little different. The goal is to reconstruct the history of the universe." Cosmology is more akin to evolutionary biology or geology, he says, in which researchers must simply accept some facts as given. For example, the theory of plate tectonics does not explain why Earth has precisely seven continents.

That distinction may disappoint the many researchers who have come to cosmology by way of physics, a field that prides itself on its rigor and unparalleled testability. Many hope to connect particle physics directly to the birth and evolution of the universe to arrive at an all-encompassing theory that, at least statistically, would allow them to mathematically derive the universe. "I don't like unexplained coincidences," Tegmark says. "Generally, I want an explanation."

To get one for the axis, many say, researchers must press on concocting new models. Others suggest looking for evidence of the axis in galaxy surveys and other types of data. A few even say that the most promising route may be to develop theories that extend to the "multiverse" of Hubble volumes beyond our own (*Science*, 23 July 2004, p. 464) and ask why the axis might help make our existence in this one more likely.

All agree that, in the end, they may never know if the axis signifies anything. "Let's face it: Nature might leave us wondering forever about certain questions," Tegmark says. We have only one universe, and in some ways perhaps it just is as it is.

–ADRIAN CHO



CREDIT: NASA/WMAP SCIENCE TEAM

Going my way? The CMB quadrupole (*top left*), octopole (*top right*), and the next two multipoles. The red dots mark their symmetry axes, which appear to line up.

EDUCATION RESEARCH

U.S. Says No to Next Global Test of Advanced Math, Science Students

After U.S. high school students did poorly on TIMSS in 1995, the government has decided not to participate in another version to be given next year

In 1995, the United States lagged behind most of the world on a test of advanced mathematics and physics taken by graduating high school students from 16 countries. That won't happen again, if the Bush Administration has its way: It has decided not to participate in the next version of the test.

The National Center for Education Statistics (NCES), part of the U.S. Department of Education's Institute of Education Sciences (IES), says it is bowing out of 2008 TIMSS-A, an advanced version of the Trends in International Mathematics and Science Study given quadrennially to younger students, because it can't fit the $5 million to $10 million price tag into its flat budget. Officials also question whether the target cohort—students finishing secondary school who have taken advanced mathematics and physics courses—is comparable around the world.

But many leaders in the mathematics community believe that the Administration opted out because it feared another poor U.S. performance would reflect badly on its signature education program, the 2002 No Child Left Behind Act. While advocates of the test look for other sources of funding, *Science* has learned that the National Board for Education Sciences, which advises IES, will ask for a review of the decision next month.

International tests have proliferated in recent years as countries seek ways to measure how well they are preparing students for jobs in a global economy. And although fourth- and eighth-grade U.S. students have performed adequately on the TIMMS tests, high school seniors have not. In 1995, the last time that cohort was measured, U.S. students topped only Austria in advanced math and ranked dead last in physics.

Planning for 2008 TIMSS-A began in 2006 at the urging of Norway and Sweden. Although 16 countries participated in the first test, only nine—the two proponents plus Russia, Italy, the Netherlands, Slovenia, Iran, Lebanon, and Armenia—have ponied up for the new test, which covers geometry, algebra, and calculus as well as mechanics, electricity and magnetism, heat and temperature, and atomic and nuclear physics. Sometime last year, NCES quietly decided not to get involved, and since then Australia, Germany, and Finland have also dropped out.

Leaders from the U.S. mathematical community, including the National Council of Teachers of Mathematics and the American Mathematical Society, are up in arms at the department's decision, first reported last month by the newspaper *Education Week*. They argue that this elite group of students needs to be monitored because they are most likely to major in STEM (science, technology, engineering, and mathematics) fields in college and become the next generation of scientists and engineers. "It's inconceivable to me that the government wouldn't fund our participation," says Stanford mathematician R. James Milgram, a member of the IES advisory board that expects to take up the issue at its 30 to 31 October meeting. "The 1995 test was extremely important in showing that a problem exists," he notes. "And the only way to know if we're beginning to turn things around is by looking at new data to see if we've made any progress."

In defending their decision, NCES officials note that they are already supporting international assessments such as the regular 2007 TIMSS for fourth and eighth graders, a fourth-grade reading exam, a math and science assessment of 15-year-olds, and a planned survey of adult literacy. They say that U.S. students may be at a disadvantage because some TIMSS-A test-takers from other countries are older and may have specialized in math and science during the latter part of their secondary school years. In addition, says NCES associate commissioner Valerie Plisko, whose office manages the various international assessments, "we typically do not benchmark against these countries."

But those explanations don't pass muster with critics. TIMSS-A "is not just a horse race," responds Patsy Wang-Iverson, coordinator of the group advocating U.S. participation and also vice president of the Gabriella and Paul Rosenbaum Foundation in Bryn Mawr, Pennsylvania, which supports mathematics education. She says there is much that U.S. educators can learn from looking more closely at this population. "A lot has changed since 1995," she says. "Students are taking more math and science and more AP [advanced placement] courses, and TIMSS-A provides us with a wonderful opportunity to evaluate their performance. If we don't do it now, we'll lose track of an entire generation of reform efforts."

After NCES bowed out, officials at the National Science Foundation (NSF) asked the Educational Testing Service (ETS) in Princeton, New Jersey, to propose how it would administer TIMSS-A. ETS's approach also would have laid the foundation for a longitudinal study of these advanced math and science students. But this summer, NSF officials declined to fund the proposal after reviewers raised questions about the target population and ETS's ability to improve on the disappointingly low levels of U.S. participation in the 1995 test. "We'd have to do more work to resolve those issues," admits ETS's Michael Nettles.

Michael Martin, co-director of the Boston College–based center that manages the international TIMMS-A assessment, says the group is on schedule to administer TIMMS-A next spring in participating countries and report the results by the end of 2009. Any change of heart by U.S. officials, he adds, won't alter that time frame. "We are sad that the United States won't be participating," Martin says. "But at some point the ship must sail."

—JEFFREY MERVIS

CREDIT: PETER HOEY

Redundancy. A positive-pressure "space suit" is one of several precautions used to protect workers from the deadliest pathogens in a biosafety level 4 lab.

BIOSAFETY BREACHES

Accidents Spur a Closer Look at Risks at Biodefense Labs

Failure to report a *Brucella* infection and other problems at a Texas university have microbiologists searching for ways to ensure safety and public trust

An unreported infection with a dangerous pathogen and other biosafety breaches at a Texas university are fueling an already heated debate about safety at U.S. biodefense labs. The problems at Texas A&M University in College Station, which led federal officials to shut down the university's biodefense research this summer, follow a spate of accidents at other U.S. labs in the past few years. They also coincide with the accidental release of foot-and-mouth virus from a research facility in the United Kingdom that has shown the potential economic devastation that can result if a pathogen escapes. These events are bringing new urgency to a question raised soon after the United States began pouring money into biodefense research after the 2001 anthrax attacks: Are the nation's biodefense labs safe enough?

"Proponents insist there is a clean safety record. That is simply wrong. With some agents, it could have catastrophic consequences," says microbiologist Richard Ebright of Rutgers University in Piscataway, New Jersey, a critic of the biodefense expansion.

Although other scientists and biosafety experts say the extensive breakdown in procedures at Texas A&M is probably exceptional, they too worry that many incidents are going unreported. Next week, a congressional committee will examine the recent accidents and the biodefense buildup.

The scrutiny is sending tremors through university administrators and the microbiology community, which is struggling with how to both ensure safety and gain the public's trust. One idea under discussion is an anonymous national accident reporting system that would enable institutions to learn from one another's mistakes.

Winning public confidence could determine whether several proposed labs, such as one being built in Boston, will be allowed to operate at biosecurity level 4 (BSL-4), the highest level used to study the most dangerous pathogens. Community support will also likely play a role in which of five competing sites wins a planned $450 million BSL-4 national agro-biodefense lab funded by the Department of Homeland Security.

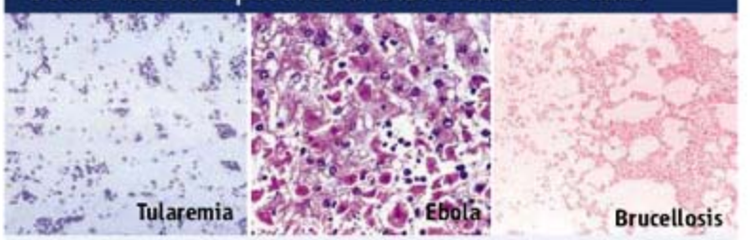
Some infectious disease experts worry that public hysteria fueled by watchdog groups over even relatively minor lab incidents will paradoxically make it harder to establish the atmosphere of trust that is essential to running a safe lab. "To ring all the bells and bring out the fire trucks is counterproductive," says virologist Clarence J. Peters of the University of Texas Medical Branch (UTMB) in Galveston. But there is room for improvement, he adds: "One of the biggest problems is transparency. I think we're all going to have to get past that."

Into the hot zone

To be sure, biosafety has come a long way in the past few decades. Before then, "there weren't a whole lot of rules, just a lot of common sense" about how to run an infectious disease lab, says virologist Charles Calisher of Colorado State University in Fort Collins, who says the biosafety officer's main message was: "Put that cigarette out; no more mouth pipetting." Peters notes that there were thousands of lab-acquired infections before the 1970s, when labs began installing hoods, shields around centrifuges, and other safeguards. In 1984, the U.S. National Institutes of Health (NIH) in Bethesda, Maryland, and Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, produced the first edition of a guidebook, called *Biosafety in Microbiological and Biomedical Laboratories* (*BMBL*), that pooled researchers' experiences and is now considered the Bible of safety.

Oversight became stricter after 2001 when federal agencies beefed up a regulation, called the select-agent rule, for the handling of pathogens such as anthrax and the Ebola virus that are potential bioweapons. The rule requires that lab workers get a security clearance for working on the roughly 80 select agents and toxins; that select-agent labs be inspected and workers undergo training; and that lab exposures and losses of select agents be reported to

Some Recent Exposures in U.S. Biodefense Labs



2002, 2003:	*E. coli* 0157:H7 infections in two USDA labs
2004:	Three workers infected with tularemia, Boston University
2004:	Ebola needle stick (no infection), USAMRIID
2004:	Anthrax exposure (no infection), Children's Hospital, Oakland, CA
2004:	Valley fever (*C. immitis*) infection, Medical College of Ohio
2005:	Potential Q fever exposure, Rocky Mountain Labs, Hamilton, MT
2006:	Brucellosis infection, Texas A&M

CREDITS (TOP TO BOTTOM): AP; CDC

CDC. About 14,000 people at 400 labs now have select-agent authorization.

To date, the most serious biosafety breaches have occurred outside the United States, such as several SARS infections in Asia in 2003 and 2004 that killed one researcher and infected several people outside the lab and the death of a Russian lab worker from Ebola in 2004. And some potential exposures—such as animal bites, needle sticks, and glove tears—are inevitable, U.S. biosafety experts say. One of the worst recent accidents occurred at the U.S. Army Medical Research Institute of Infectious Diseases in Fort Detrick, Maryland, where a worker was exposed to the Ebola virus but didn't become infected. Others (see table, p. 1852) involved shipments of pathogens labeled nonpathogenic that turned out to be virulent. That happened with tularemia in Boston University in 2004, where three workers were infected. The incident was reported to local authorities and made public only after delays, adding to criticism of the proposed Boston BSL-4 lab (*Science*, 28 January 2005, p. 501).

The problems at Texas A&M, however, may be the most egregious to date. They first emerged in April when the school belatedly reported to CDC that in February 2006, a worker was infected with *Brucella* bacteria, a pathogen common in livestock that causes fever and fatigue in humans but is rarely fatal. This incident, like many others, was brought to light through public records requests by Edward Hammond of the Sunshine Project, a watchdog group in Austin, Texas. In June, after the Sunshine Project reported that three workers had tested positive for antibodies to the Q fever pathogen, CDC shut down all of Texas A&M's select-agent work. In an August investigation, CDC inspectors found a dozen serious violations, including unapproved experiments, lost samples, improper safety training, and lab workers without select-agent authorization (*Science*, 14 September, p. 1487).

Some observers suggest the Q fever antibody tests were not a major issue; none of the workers became ill, and two were apparently exposed before they joined the lab. But the *Brucella* case, which happened when a worker leaned into an aerosol chamber to clean it, is a clear violation of safe practices: The chamber should have been decontaminated with gas first, says Jonathan Richmond, a consultant in Southport, North Carolina, who oversaw biosafety at CDC in the 1990s. It has added to speculation that more incidents aren't being reported. Hammond has used open-records requests to dig up examples of exposures, equipment failures, and other near-misses at various labs that weren't publicly disclosed. He says they suggest other significant mishaps are hidden.

Researchers and biosecurity experts say serious infections would be difficult to hide from CDC. But some agree there is probably underreporting of mild infections and potential exposures. Workers who make a mistake are often embarrassed and may fear angering their supervisor, and institutions worry about the damage to their reputation, says Richmond. "It's been a problem for a long time," he says. Supporting that suspicion, CDC, which has recorded about 20 accident reports a year since 2004, has received 32 reports since April 2007, possibly because of the publicity about Texas A&M, says a CDC spokesperson.

Although the multiple protocol violations at Texas A&M may be the exception, less extensive violations are not. A 2006 Department of Health and Human Services (HHS) Inspector General audit of security procedures found that 11 of 15 institutions had "serious weaknesses" such as unlocked doors and freezers and lax inventory records. Janet Shoemaker, public affairs director for the American Society for Microbiology in Washington, D.C., points out that schools have a strong incentive to adhere to the rules; since 2003, the HHS Inspector General has levied fines ranging from $12,000 to $150,000 on nine research institutions and companies for breaches such as unapproved select-agent shipments. Texas A&M is facing fines as high as $500,000 for each violation.

No public menace

One point of agreement among most scientists is that however scary these incidents sound—the mention of Ebola virus conjures the 1995 movie *Outbreak*, for example—the risk to the public is very low for most pathogens, for two reasons. First, there have been no known environmental escapes from BSL-4 labs since the early 1980s and only two workers are known to have become infected in BSL-4 labs, both outside the United States. Workers have many layers of protection, including positive-pressure "space suits," and realize the hazards of working with pathogens studied in BSL-4 labs, for which, by definition, there are no treatments.

Second, even if an agent studied in a BSL-4 lab did escape, most, with the exception of smallpox (which can only be studied at CDC), are not very transmissible. Anthrax doesn't spread person to person, for example. Ebola and other hemorrhagic fevers that have killed hundreds in Africa would likely never cause an outbreak in Western countries because hygiene and medical treatments are so much better, says Peters. (He also notes that many select agents, such as anthrax and Q fever, occur commonly in nature, so people

Proliferation. Critics are worried about the potential for infections and escapes at biosafety level 4 (BSL-4) labs (five existing, at six least planned) and 84 existing and new BSL-3 biodefense labs, as compiled here by the Sunshine Project.

SOURCE: THE SUNSHINE PROJECT, WWW.SUNSHINE-PROJECT.ORG AS OF FEBRUARY 2006

can get infected without coming anywhere near a biodefense lab.)

Some scientists and biosafety experts are more worried about risks at BSL-3 labs, because the standards at these labs are not as stringent. But even most of these pathogens—with the exception of SARS, avian influenza, and 1918 flu—are not very communicable, and in any case vaccines and other treatments are available. At most, says infectious disease modeler Ira Longini of the University of Washington, Seattle, "the result could be a handful of cases and maybe deaths." Another exception is foot-and-mouth disease, which doesn't infect humans but is extremely contagious among animals; the escape in the United Kingdom, which has been tied to an outdated effluent treatment system, would be unlikely to occur at more modern facilities in the United States, Richmond says.

Peters worries that the "hysteria and witch hunting" by people like Hammond of the Sunshine Project is compromising safety by making lab workers worry that reporting potential exposures will get them fired. "People can't be terrified to report," agrees Jean Patterson of the Southwest Foundation for Biomedical Research in San Antonio, Texas, which runs a BSL-4 lab.

Safety check

So how can biosafety be improved? One proposal is an anonymous, mandatory reporting system for all laboratory accidents. Such a system would enable labs to learn from one another's mistakes, as do the data compiled on aviation accidents by the National Transportation Safety Board, says Gigi Kwik Gronvall of the Center for Biosecurity of the University of Pittsburgh Medical Center in Baltimore, Maryland, who co-authored a paper describing this proposal earlier this year in *Biosecurity and Bioterrorism*. "Other industries have gone through this," says Gronvall. The system would also capture lab exposures to pathogens not on the select-agent list, such as HIV and tuberculosis. Reporting these to NIH or CDC is not mandatory, Rutgers's Ebright notes.

But some microbiologists caution that reportable incidents should be well-defined, lest the system become glutted with minor mishaps. (Peters cites UTMB's recent decision to release, at a community group's request, a list of its 17 near-misses in the past 5 years.) Also important, says biosafety consultant W. Emmett Barkley of Bethesda, Maryland, reports should include not just bare facts but analysis, as CDC now provides for selected lab accidents in its *Morbidity and Mortality Weekly Report*.

A more radical idea is to require that BSL-3 and BSL-4 labs be licensed by the federal government. This would mean that all these labs, not just those working on select agents, would be inspected and they would be required to follow the same operating procedures. One supporter of this proposal, biosecurity expert Anthony Della-Porta of Geelong, Australia, says the problem now is that *BMBL* offers only general guidance. Others, such as Barkley, say institutions need flexibility, especially the many BSL-3 labs that don't do biodefense work.

There's one fact that nobody disputes: The risk of accidents in biosafety labs goes up with the number of workers. For that reason, watchdog groups and even some biodefense researchers lament the lack of analysis on whether all of the six planned BSL-4 and two dozen new BSL-3 biodefense labs are actually necessary to protect the nation from bioterrorism (see map). Says Gronvall: "Is there too much [biodefense research]? Without seeing the plan of action, it's hard to say."

–JOCELYN KAISER

ECOLOGY

Setting the Forest Alight

To validate satellite data for carbon-emissions modeling, researchers this summer torched a jack-pine forest in Canada and tried to ignite a stand of larch in Siberia

KODINSK, RUSSIA—In July, as temperatures soared during a heat wave in eastern Siberia, scores of large fires flared through the region's dense pine forests. For 500 kilometers along the Amur River northwest of Lake Baikal, thick smoke blanketed the wilderness. Officials with Russia's famous airborne forest fire fighting service, Aviale-sookhrana, were tracking the wildfires at an airbase here in Kodinsk, a small city on the Amur. They were tense. To them it seemed bizarre that a team of international scientists had received permission to burn a patch of nearby forest. Even with every local helicopter and plane conscripted to serve their firefighting crews, millions of dollars' worth of timber was going up in smoke in wildfires. "It's not as though we don't have enough to worry about already," mused Oleg Mityagin, the overtaxed local Avialesookhrana boss. "We're in no position to help them if they lose control."

Safe distance. Douglas McRae checks out a gap in a pine forest during an experimental burn in Ontario, Canada.

CREDIT: PAUL WEBSTER

Sixty kilometers to the west at the experimental site, a group of Russian, American, and Canadian researchers hoped to set a test fire that would thoroughly burn a hectare-sized patch of larch forest, Siberia's dominant conifer. Their aim was to quantify carbon emissions from fires in larch forests across Siberia, now inadequately documented, according to Douglas McRae, a forest-fire researcher with the Canadian Forest Service. McRae has been conducting experimental burns in Canada and Russia since 1999 as part of project FIRE BEAR (Fire Effects in the Boreal Eurasia Region), a research program aimed at studying forest-fire behavior, ecological effects, emissions, carbon cycling, and remote sensing.

Conceived in 1997, FIRE BEAR brings researchers from the U.S. Department of Agriculture (USDA) Forest Service and the Canadian Forest Service together with colleagues at the Siberian branch of the Russian Academy of Sciences' (RAS's) V. N. Sukachev Institute in Krasnoyarsk. As the group's previous studies have shown, extreme forest fires are growing more frequent in Siberia. And some models predict that climate change will bring dramatic warming—and more forest destruction—in eastern Siberia and other northern regions. The experimental burn, the FIRE BEAR team hoped, would yield direct observations to buttress satellite data and fill gaps in the models.

Hot results. A sudden gust of wind sent flames temporarily out of control in a Canadian test area, but the fire produced terrific data.

CREDIT: PAUL WEBSTER

Flaming wilderness

The searing summer heat in Kodinsk presented a dilemma for the scientific team. "We want the larch to burn well in order to obtain good data," McRae explained, "but we risk losing control if it burns a little too well." In the days leading up to the experimental burn, bulldozers hacked firebreak lanes around the test patch, and researchers wired the forest floor with probes to gauge heat release, carbon emissions, and effects on vegetation and microbes. McRae had good reason to be anxious. In May, in similar weather, he and his FIRE BEAR colleagues conducted an experimental burn near Sault Ste. Marie, Canada, in which a hectare-sized patch of bone-dry jack-pine forest fanned out of control. That experiment was meant to show how infrared technology can be used to estimate fuel consumption and carbon emissions during fires. McRae and his colleagues hoped it would help them gauge how Russian wildfires contribute to greenhouse gas emissions. (Russian security laws prevent infrared filming from the air.)

Only minutes before the scientists ignited the fire in Ontario, wind gusts unexpectedly blew through the treetops. After ignition, the entire test plot flared in an explosive burst that melted computerized monitoring equipment. The equipment technicians got out unharmed with much of the damaged, although still-functioning, gear belonging to Martin Wooster, a geographer at King's College London.

Wooster believes that the amount of carbon emitted from wildfires every year is possibly half that released by fossil-fuel consumption. He has been traveling the world collecting data to confirm his theory. In the Canadian test, he had an opportunity to gather data at ground level and at 300 meters above the fire in a helicopter. Researchers will use the observations to test the accuracy of satellite data.

While making an infrared film, Wooster watched the test fire jump across the firebreaks around the experimental site. Within a few hours, more than 1400 hectares of magnificent pine forests were ablaze. Water bombers, surveillance planes, and Wooster's rented helicopter scrambled to get the situation under control. Wooster came away with an impressive data haul that will help to validate the usefulness of infrared measurement, he said later. But Ontario forest officials were not pleased. "I strongly doubt they'll be quick to give permission for more such experimental fires in future," Wooster said.

Foresters aren't the only ones to express doubts; Russian security officials have been wary, too. Thanks to an infusion of funding from the International Science and Technology Center in Moscow, which supports nonmilitary collaboration between Western scientists and those within the Russian weapons complex, FIRE BEAR has attracted former-Soviet military experts in remote sensing. Other scientists have joined, including members of the Siberian RAS's Institute of Chemical Kinetics and Combustion in Novosibirsk, as well as U.S. researchers funded by NASA.

Some Russians have complained of being arrested and undergoing harrowingly long interviews, says Anatoly Sukhinin, a remote-sensing expert who joined FIRE BEAR after a career in the Soviet military. "I still spend a fair amount of my time explaining our work to the police," complained Sukhinin, sitting in his laboratory in Krasnoyarsk, which NASA helped equip to receive and interpret Siberian fire data beamed from American and Russian satellites. "It doesn't help that we're doing these experiments in a region which was until recently secret and still remains heavily militarized."

Despite the hassles, the partnership seems to be paying off. In recent years, says Amber Soja, a research scientist with the U.S. National Institute of Aerospace, currently resident in the Climate Dynamics branch of NASA's Langley Research Center in Hampton, Virginia, FIRE BEAR papers have widened knowledge of Siberian forest fires and their global atmospheric effects. In 1998, Brian Stocks of the Canadian Forest Service reported a positive correlation between climate-change impacts and an increase in the severity of Siberian fires. A 2004 paper by Soja, along with McRae, Sukhinin, and Susan Conard of the USDA Forest Service, concluded that disparities in the amount of carbon stored in different forest types and the severity of fires within them can affect total direct carbon emissions by as much as 50%. This is why they need specific data on larch fires, which emit less carbon than pine. In extreme fire years, they found, total direct carbon emissions from wildfires can be 37% to 41% greater than in normal ones, because severer fires consume more organic matter in the forest floor.

Last year, Soja, Stocks, and Sukhinin published a review of predictions of climate-induced boreal forest change. Four of seven models predict that warming in Siberia will be 40% greater than the global mean. Soja spent several weeks at the FIRE BEAR camp near Kodinsk last summer, living in a tent and subsisting largely on tinned fish and buckwheat cereal while comparing notes with her Canadian and Russian co-investigators in the run-up the test burn. The predictions she co-reviewed, she says, are already coming true in Alaska, Canada, and Russia. In Siberia, 7 of the last 9 years have resulted in extreme fire seasons, she explains. Speaking from the camp, she said, "If you are looking for climate-change impacts on forests, this is the place to be."

On the day of the big test burn this summer in Kodinsk, however, all predictions went up in smoke. Minutes after local fire crews ignited the perimeter of the experimental larch site with benzene, dark clouds suddenly appeared and rain doused the flames. "You'd be surprised how often this sort of thing happens," McRae said with a shrug. "That's what you get for playing with fire." The researchers, who still need the larch data, are already planning to torch a forest in Siberia next summer.

–PAUL WEBSTER

Paul Webster writes from Toronto, Canada.

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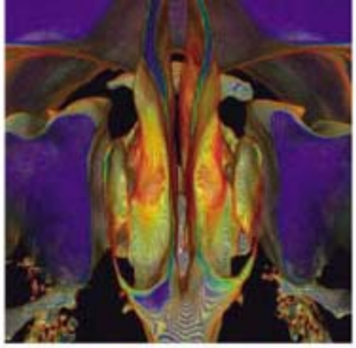
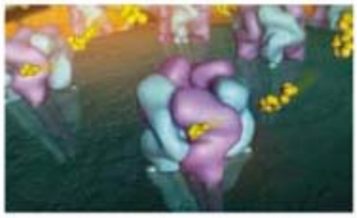
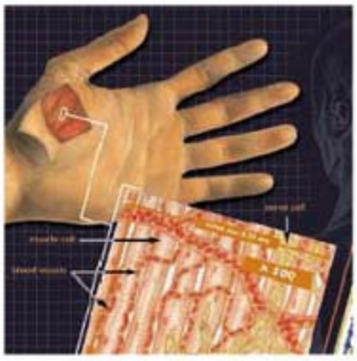






2007 Visualization Challenge

SCIENTIFIC DATA ARE THE CURRENCY OF science, but they often buy little understanding outside science itself—or even outside the narrow confines of a single scientific discipline. But when data are brought to life through images, illustrations, computer graphics, and animations, they can stimulate excitement, awe, new ways of looking at things, and, above all, a broad appreciation of even the most esoteric scientific information. The stunning photograph on the cover of this week's issue of *Science* is a case in point. It reveals the humble and ubiquitous seaweed Irish moss (*Chondrus crispus*) to be an intricate natural construction that looks for all the world like an abstract painting.

For the past 5 years, *Science* and the National Science Foundation (NSF) have cosponsored annual challenges to encourage cutting-edge efforts to visualize scientific data. Our interest in supporting these competitions is based on our firm belief that bringing data to life visually will be increasingly important not only for public understanding of science and engineering but also for improving communication across scientific disciplines.

This year, we received more than 200 entries from 34 states and 23 countries representing every continent except Antarctica. A committee of staff members from *Science* and NSF screened the entries, and an outside panel of experts in scientific visualization reviewed the finalists and selected the winners. The winning entries appear on the following pages. (No awards were made this year for illustration.)

We encourage you to submit applications for next year's challenge, details of which will be available at www.nsf.gov/news/special_reports/scivis/index.jsp, and to join us in celebrating this year's winners.

Susan Mason of NSF organized this year's challenge. Benjamin Lester of *Science*'s news staff wrote the text that accompanies the images in this special section, and Stewart Wills and Tara Marathe put together a special Web presentation at www.sciencemag.org/sciext/vis2007.

JEFF NESBIT, DIRECTOR, OFFICE OF LEGISLATIVE AND PUBLIC AFFAIRS, NSF
MONICA BRADFORD, EXECUTIVE EDITOR, *SCIENCE*

Science NSF

JUDGES

(pictured left to right)

FELICE FRANKEL
Senior Research Fellow, FAS
Harvard University
Initiative in Innovative Computing
Cambridge, Massachusetts

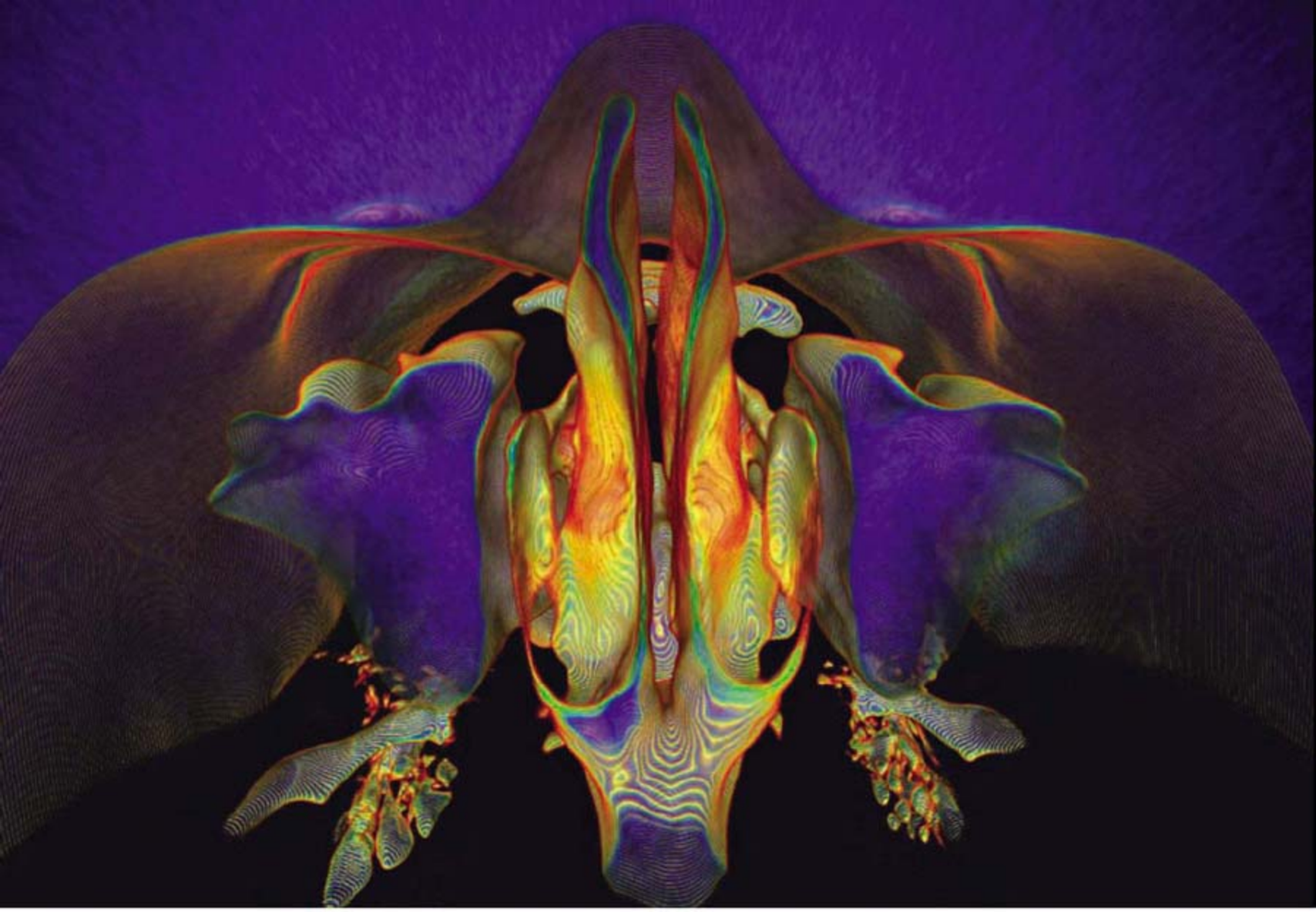
THOMAS LUCAS
Thomas Lucas Productions Inc.
Ossining, New York

SHERRY A. MARTS
Vice President, Scientific Affairs
Society for Women's Health Research
Washington, D.C.

GARY LEES
Chairman & Director
Department of Art as Applied to Medicine
Johns Hopkins School of Medicine
Baltimore, Maryland

PATTERSON CLARK
The Washington Post
Washington, D.C.

CREDIT: P. OLMERT/NSF



Photography

FIRST PLACE (TIE)

WHAT LIES BEHIND OUR NOSE?

Kai-hung Fung, Pamela Youde Nethersole Eastern Hospital

HUMAN ANATOMY IT MAY BE, BUT THE AIRWAYS THAT RIDDLE THE SPACE BEHIND OUR noses take on an alien aspect in this unearthly rendering created by Kai-hung Fung, a radiologist at the Pamela Youde Nethersole Eastern Hospital in Hong Kong.

A computed tomography (CT) scan from a 33-year-old Chinese woman being examined for thyroid disease provided the raw data for Fung's rendering. He stacked together 182 thin CT "slices" to create a 3D image looking upward at the sinuses from underneath the head.

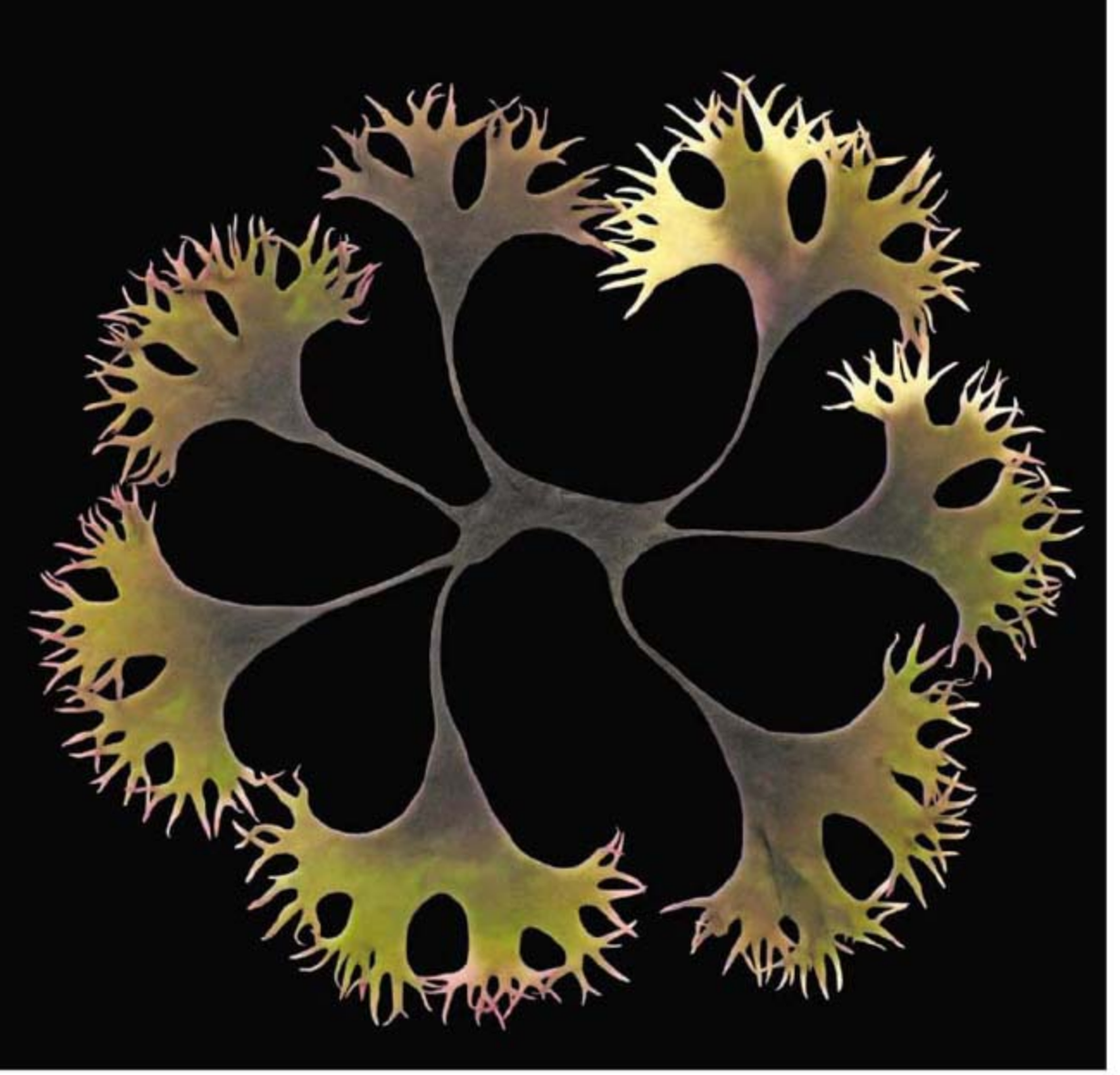
Fung chose to use the patient's CT images for his rendering, he remembers, because "[she had] a very straight nasal septum and wavy maxillary sinuses; … the anatomy was exceptionally beautiful," he says.

Normally, CT renderings meld slices together into smooth surfaces, but, in what he terms the "Rainbow Technique," Fung instead broke them apart, creating a topographical map of the airspaces described by the contour lines of individual slices, and colored according to the density of the tissues that border them.

Fung digitally removed the bones, soft tissue, and fat from the rendering to create a solid "cast" of the sinuses' air envelope. "The sinuses are hollows in the bone just like the central cavity in a papaya," he says. One way to get a feel for the shape of such a cavity is to look at a cross section of it, but, he says, it's much more readily apparent in a mold.

The upward-looking angle that Fung used was fascinating, says panel of judges member Sherry Marts. "You react [to the image] on two levels; it piques your curiosity … and then draws you in to the information that's contained in [it]."

2007 Visualization Challenge



FIRST PLACE (TIE)

IRISH MOSS, *CHONDRUS CRISPUS*

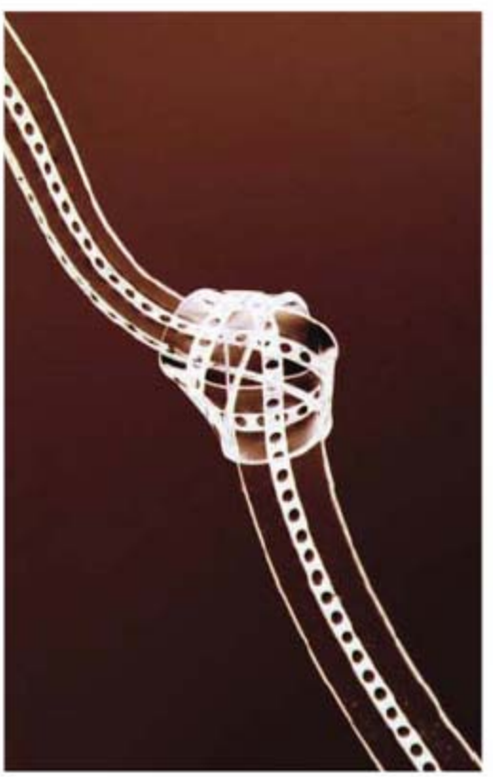
Andrea Ottesen, University of Maryland

THE SLIMY, GLISTENING MASS OF seaweed washed up on a sandy beach seems light-years distant from this feathery, dendritic image of Irish moss (*Chondrus crispus*) created by Andrea Ottesen, a botanist and molecular ecologist at the University of Maryland, College Park. "If you pull *Chondrus* out of the ocean, it's folded on itself—really curled up," she says. It wasn't until after she had "pressed every one of those little ends down with sea stones" and left it to dry for 2 days that the seaweed's beautiful, simple shape was revealed.

Ottesen uses only a black background, a Canon ELPH 7-megapixel digital point-and-shoot camera, and natural lighting to photograph many of the plants she encounters in her work. Her winning photo shows a piece of Irish moss she collected off the coast of Cape Breton Island, Nova Scotia, while cataloging the use of kelp products as fertilizers for a sustainable agriculture experiment. "You can get just as good light—or even better—with natural light" than with strobes and spotlights, she says.

The 15-centimeter-wide red algae seems exotic in this abstract portrait, but it is ubiquitous both in nature and in our day-to-day lives. Besides being one of the most common seaweed species on the Atlantic coast, says Ottesen, Irish moss and algae like it are sources of natural thickeners and stabilizers called carrageenans, which are widely used in processed foods as diverse as lunch meat and ice cream.

"There was this gasp when this photo came up on the screen," says panel of judges member Felice Frankel. "We shouldn't forget that we don't need [complex equipment and techniques] to create beautiful representations."



HONORABLE MENTION

TINY METAL PATHWAYS

Adam C. Siegel and George M. Whitesides, Harvard University

IT'S NOT OFTEN YOU SEE A WIRE INTENTIONALLY tied into a knot, especially when that wire is a state-of-the-art microstructure only 200 micrometers wide. However, Adam Siegel and colleagues at Harvard University tangled up their invention to prove a point: Flexibility is key to integrating microelectrical circuits into fabrics, according to Siegel. Rather than extruding the wire, Siegel and colleagues poured molten indium/tin solder into a microfluidic channel in clear silicon and allowed it to cool. Depending on the solder composition, he says, the wire can be solid or flexible, and any breaks can be healed by simply reheating it.

FIRST PLACE

MODELING THE FLIGHT OF A BAT

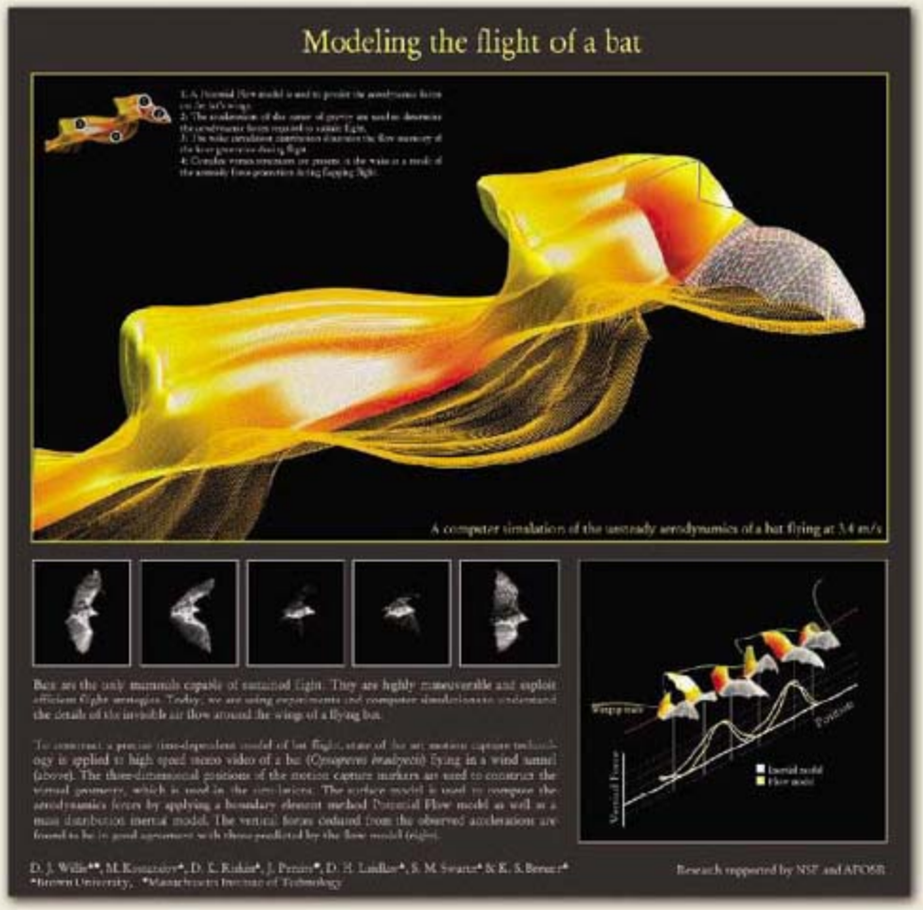
David J. Willis, Brown University/MIT, and Mykhaylo Kostandov, Brown University

MOST SHORT-NOSED FRUIT BATS (*Cynopterus brachyotis*) spend their nights flitting about in the jungles of Southeast Asia. However, some of the tiny creatures, which weigh less than 50 grams fully grown, lead an altogether different existence: flitting about in wind tunnels under the watchful eyes of aerodynamics researchers.

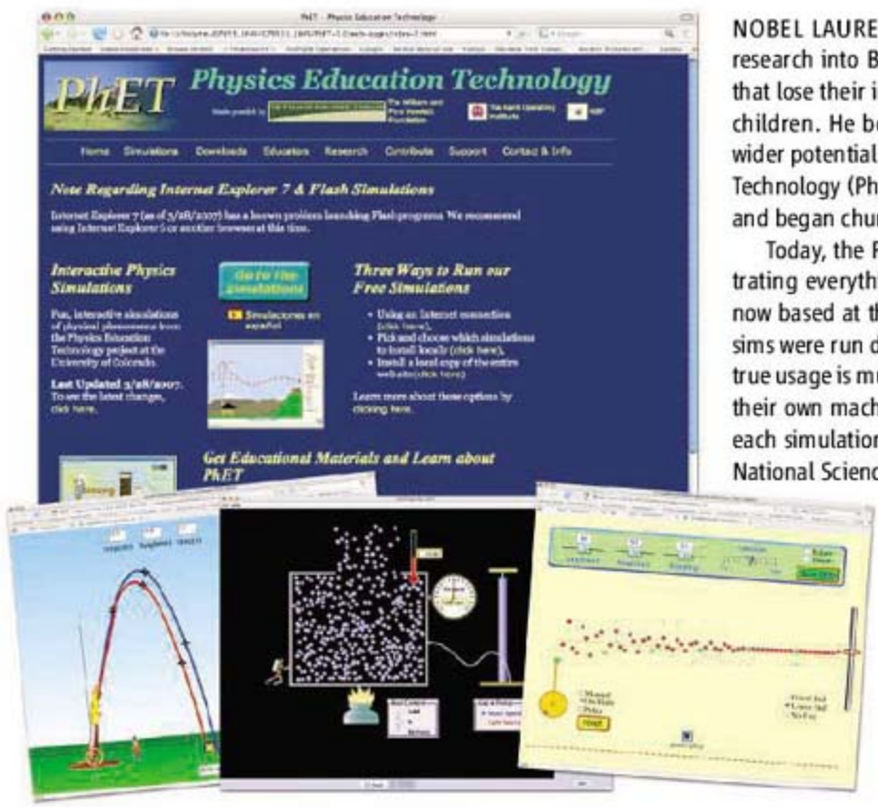
Interested in the tiny mammals' flight dynamics, Brown University engineer Kenneth Breuer used lasers and a sophisticated multicamera motion-tracking system to record how their wings and the air around them distorted as the animals flapped against the wind. Based on the experiments, aeronautical engineer David Willis, who has a joint appointment at Brown and MIT, Brown computer scientist Mykhaylo Kostandov, and their colleagues created a computer model of bat flight—visually conveyed in this poster.

"When viewed in slow motion," says Willis, "bat flight is beautiful and complex. The goal of this illustration is to capture that beauty while also adding scientific merit."

"You didn't have to read anything; the poster conveyed information … from across the room," says panel of judges member Sherry Marts. Judge Gary Lees likens the main image to "silk blowing in the wind."



Interactive Media



NOBEL LAUREATE CARL WIEMAN WAS LOOKING FOR A WAY TO EXPLAIN HIS research into Bose-Einstein condensates—strange assemblies of supercold atoms that lose their individuality and form "superatoms"—to both physicists and schoolchildren. He began creating computer simulations, but he swiftly realized their wider potential for teaching physics of all types and initiated the Physics Education Technology (PhET) project at his then-home of the University of Colorado, Boulder, and began churning out simulations.

Today, the PhET Web site lists 65 simulations available for free download, illustrating everything from quantum tunneling to projectile motion. Wieman, who is now based at the University of British Columbia in Vancouver, says several million sims were run directly off the Web site in the first 6 months of this year, but says the true usage is much higher, because most people download the sims and run them off their own machines. At a cost of between $10,000 and $50,000 to create and test each simulation, the project is a considerable enterprise, bankrolled at first by the National Science Foundation and later by a medley of sources, including Wieman's own Nobel money. "They're not cheap to do right," he says.

However, Wieman and team got what they paid for. "Some of the principles of physics have never been as well depicted and elucidated," says panel of judges member Gary Lees.

FIRST PLACE

PHYSICS EDUCATION TECHNOLOGY PROJECT (PhET)

Carl Wieman and the PhET team, Univ. of Colorado, Boulder

Informational Graphics

WHAT TIES LIFE FORMS TOGETHER? Visitors to the Exploratorium in San Francisco, California, discover that life has four basic traits: Life needs energy; all life shares common materials; life creates more life; and life changes over time. Unveiled in 2003, the "Traits of Life" exhibit has been hugely popular, even spawning a traveling road show. This poster sprang from the drive to provide examples of the ways in which life uses energy. Geared toward high school students, it explains the cycle that muscles use to "turn energy into motion."

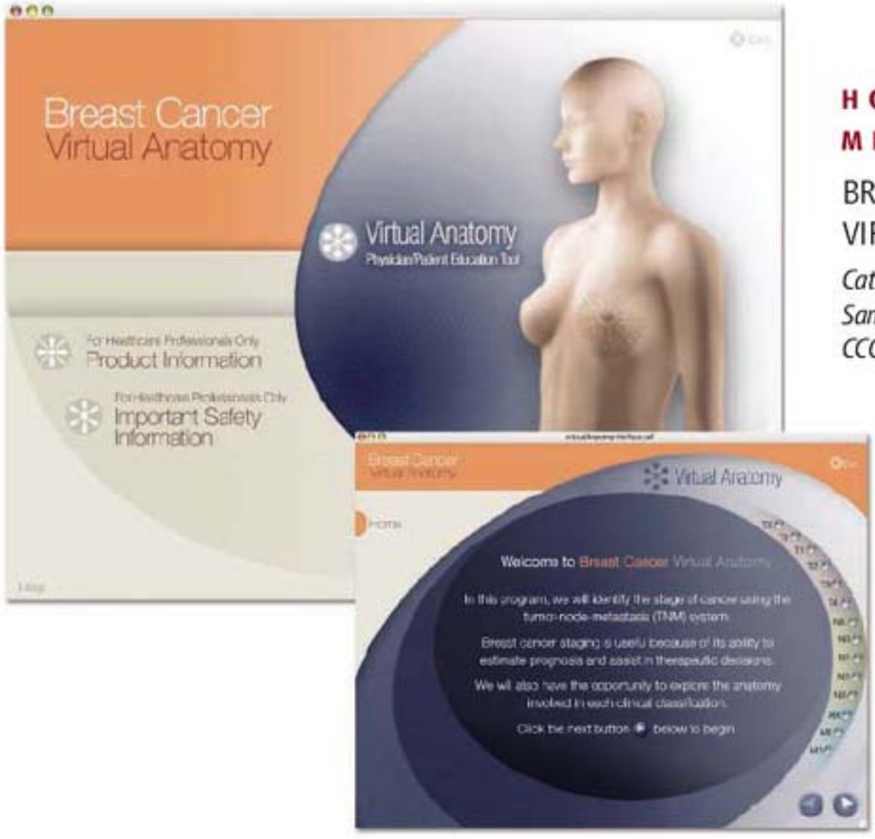
Graphic designer Mark McGowan, scientific illustrator David Goodsell, and their Exploratorium colleagues use the example of gripping a baseball to explain how muscles work. Zooming in on a chunk of hand muscle with a magnification power of 200,000, the exactly scaled poster shows how club-headed molecules of myosin use energy from ATP to repeatedly grab long filaments of actin and drag them toward each other "like a ship's crew pulling a rope hand over hand." Repeated trillions of times in all the muscle fibers of the hand, the result is a baseball that doesn't fall to the floor.

The Exploratorium has distributed the poster widely, in part by including it in the winter 2003 issue of *Exploratorium Quarterly*, to nearly 20,000 members, subscribers, and teachers.

HONORABLE MENTION

HOW DOES A MUSCLE WORK?

Mark McGowan and David Goodsell, Exploratorium



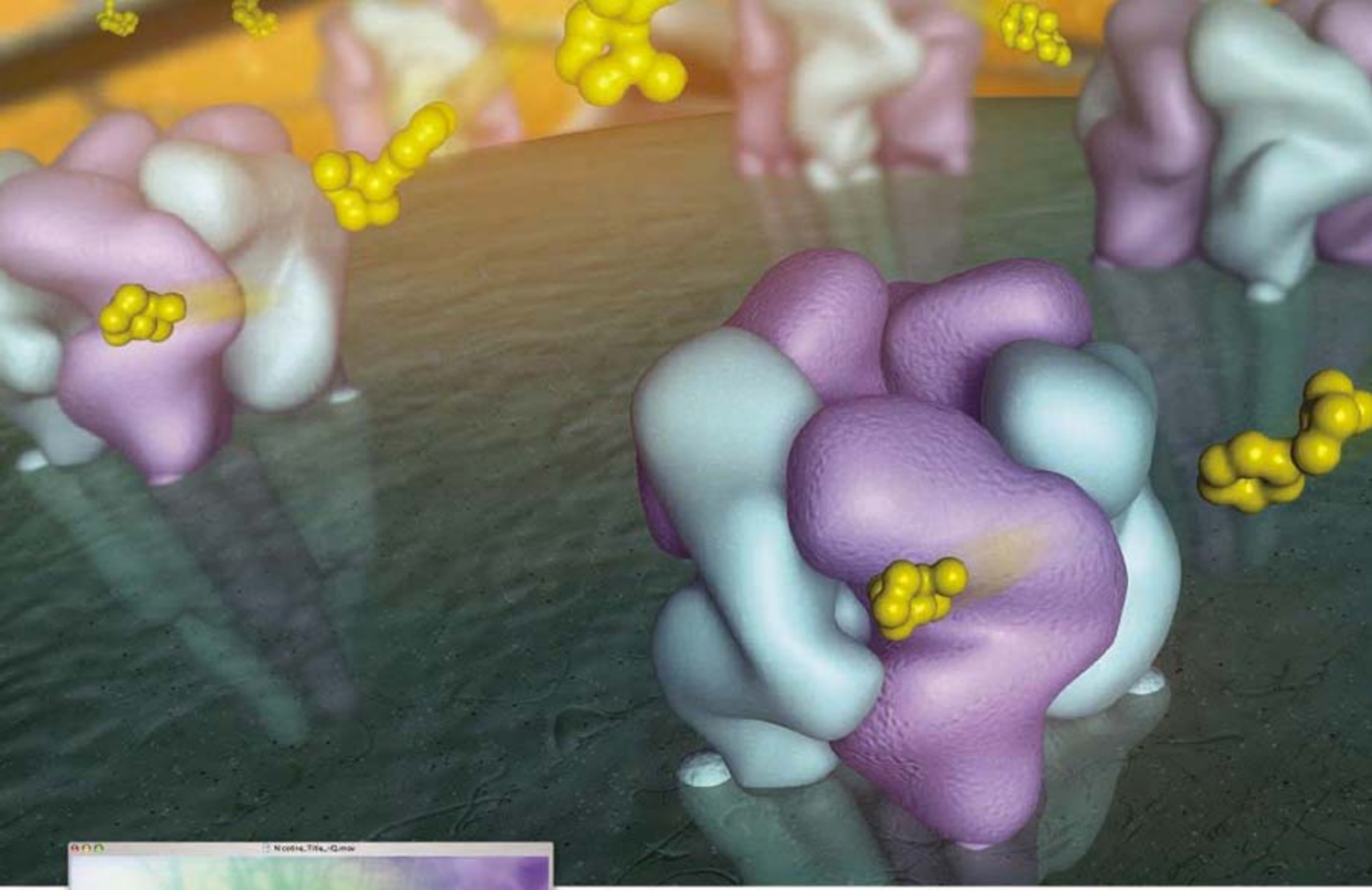
HONORABLE MENTION

BREAST CANCER VIRTUAL ANATOMY

Cathryn Tune and Samantha Belmont, CCG Metamedia

A VISIT TO THE DOCTOR'S office can be a scary, confusing experience, particularly when the subject under discussion is chemotherapy's failure to eradicate breast cancer. Cathryn Tune, Samantha Belmont, and their team at CCG Metamedia, a medical education company based in New York City, created this interactive tool to help doctors explain to their patients the anatomy and progression of their cancers in a clear, easy-to-understand manner. The interface allows doctors to select tumor size and level of metastasis and displays the part of the patient's anatomy that cancer is attacking while suggesting treatment options.

The program was created to promote Abraxane, an injectable drug designed to treat patients whose chemotherapy has failed, and was distributed to oncologists during an educational course titled "Difficult Cases in Metastatic Breast Cancer," funded by Abraxis BioScience, the drug's developer.



2007 Visualization Challenge

Noninteractive Media

FIRST PLACE

NICOTINE: THE PHYSIOLOGIC MECHANISM OF TOBACCO DEPENDENCE

Donna DeSmet and Jason Guerrero, Hurd Studios

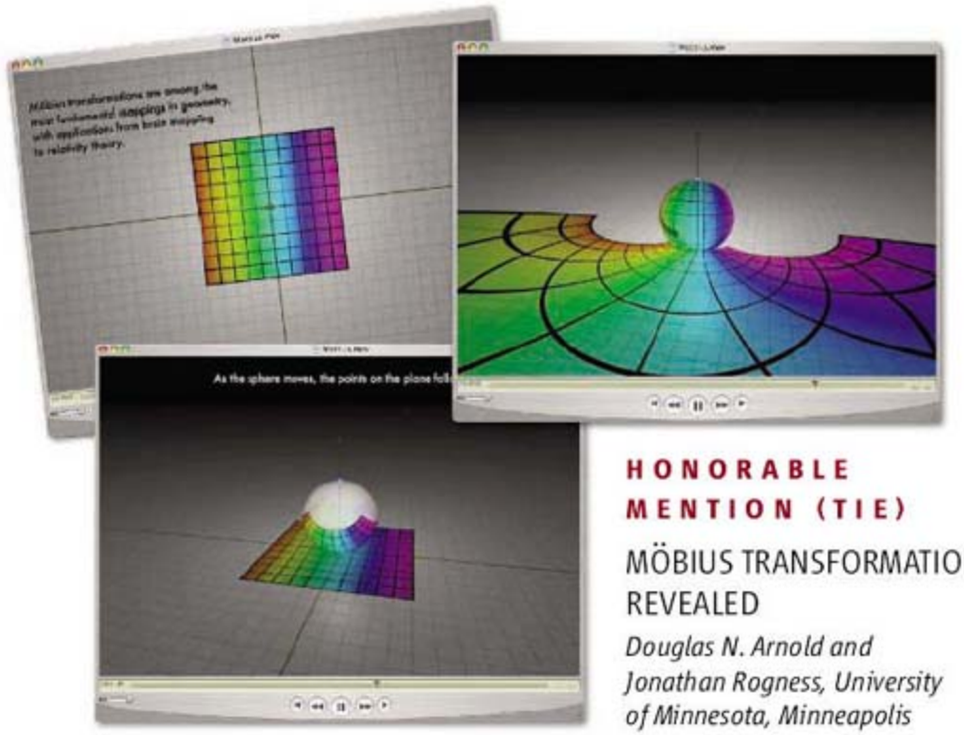
WITH EVERY DRAG A SMOKER TAKES, TRILLIONS OF NICOTINE molecules rush from the lungs to the bloodstream and into the brain, where they bind to $\alpha 4\beta 2$ nicotinic acetylcholine receptors and stimulate the release of pleasure-inducing dopamine. But as nicotine is eliminated, dopamine levels fall, and smokers begin to crave another dose.

Over time, the brain becomes dependent on the drug, and the result is an addiction that claims 4 million lives a year from emphysema, lung cancer, heart disease, and other smoking-related diseases.

That is the message of this video, created by art director Donna DeSmet, animator Jason Guerrero, and their team at New York City–based Hurd Studios, a scientific visualization company specializing in "cutting-edge science with educational aspects," according to president Jane Hurd.

The video was distributed to physicians worldwide as part of an educational course funded by the pharmaceutical company Pfizer, which manufactures the smoking-cessation drug Chantix.

Panel of judges member Gary Lees was impressed with the direct simplicity of the video. "[The video] pulled it together," he says, "from the outside world to the molecular level of the addiction."



HONORABLE MENTION (TIE)

MÖBIUS TRANSFORMATIONS REVEALED

Douglas N. Arnold and Jonathan Rogness, University of Minnesota, Minneapolis

ANY REAL NUMBER CAN BE PLOTTED ON A LINE THAT RUNS FROM NEGATIVE TO POSITIVE infinity, but throw in an imaginary component and the line becomes a plane, where complex numbers are plotted on both the real and the imaginary axes. Möbius transformations are mathematical functions that send each point on such a plane to a corresponding point somewhere else on the plane, either by rotation, translation, inversion, or dilation. It may sound confusing, but after watching this simple and elegant explanation of Möbius transformations created by Douglas N. Arnold and Jonathan Rogness of the University of Minnesota, Minneapolis, everything becomes clear. Set to classical music, the video demonstrates the transformations in two dimensions but then backs away and adds a third—placing a sphere above the plane and shining light through it. As the sphere moves and rotates above the plane, suddenly all the transformations become linked, in a way that conveys visually in minutes what would otherwise take "pages of algebraic manipulations" to explain, says Rogness.

HONORABLE MENTION (TIE)

TOWERS IN THE TEMPEST

Gregory W. Shirah and Lori K. Perkins, NASA/GSFC

THE CENTER OF A HURRICANE'S eye may be calm, but its walls are anything but. As NASA's Tropical Rainfall Measuring Mission satellite orbited above the Caribbean in 1998, it captured radar images of vast clouds dubbed "hot towers," stretching up nearly 18 kilometers into the sky, in the eye wall of Hurricane Bonnie as the hurricane moved northwest along the northern edge of the Bahamas. In "Towers in the Tempest," Gregory W. Shirah, Lori K. Perkins, and their colleagues at NASA's Goddard Space Flight Center in Greenbelt, Maryland, use satellite imagery and supercomputer simulations to reveal these hot towers as the hurricane's "express elevators," intensifying the storm as they launch swirling air from the storm's base up all the way to the edge of the stratosphere at 18,000 meters.

LETTERS

edited by Jennifer Sills

Birds Like Music, Too

IN THE RANDOM SAMPLES ITEM "MONKEYS HAVE TIN EARS" ON A recent study by Joshua McDermott and Marc Hauser (*1*), Isabelle Peretz is quoted as saying, "The observations suggest that only humans have a natural, or innate, inclination to engage with music" (3 August, p. 577). This statement is not quite true. McDermott and Hauser have shown a difference between how humans and nonhuman primates respond to music, but they have not shown a difference between humans and all other animals. It is a well-known phenomenon that birds use song to communicate. Whether birdsong is considered music is still debatable; however, the many parallels between birdsong, language, and music have been, and are still, extensively studied. Certainly, there are similarities between humans and songbirds in their ability to discriminate and respond to music. For example, Watanabe and Sato (*2*) have shown that Java sparrows can discriminate between Bach's French Suite no. 5 in G minor and Arnold Schoenberg's Suite for Piano opus 25. The birds were also able to generalize new music by Bach (Orchestral Suite No. 3 in D major) and Schoenberg (Five Orchestra Pieces, Opus 16) and artists in similar categories, i.e., Vivaldi and Elliott Carter. In these experiments, music by Bach and Vivaldi was considered classical music, while the music of Schoenberg and Carter was considered modern music. Watanabe and Nemoto (*3*) have also shown that, given the option of three perches producing either silence, classical, or modern music, the Java sparrows preferred Bach to Schoenberg and Vivaldi to Carter. These results indicate that Java sparrows or songbirds prefer classical to modern music, or perhaps just more harmonious to dissonant sounds. Additionally, the sparrows chose music they "liked" (e.g., Bach) over silence or music they "disliked" (e.g., Schoenberg). These findings resemble those of McDermott and Hauser and suggest that birds, like humans, clearly engage, and are inclined to engage, with music.

AUSTEN GESS

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Climate Change: Don't Forfeit the Game

THE ATMOSPHERE HAS A BOTTOM LINE FOR THE United States Congress: By 2050, we need to cut our output of greenhouse gases to about 20% of our 2004 levels. A bill considered in a recent *Science* Editorial ("Climate: Game over," D. Kennedy, 27 July, p. 425) as most likely to become law does not cut emissions enough to achieve that goal. The flaw in this legislation, drafted by Senators Jeff Bingaman (D-NM) and Arlen Specter (R-PA), is that it includes a large loophole called a "safety valve." If it costs more than $12 for emitters to cut one ton of carbon emissions (a likely scenario), the cap is lifted, polluters can spew without limit, and emissions will continue to rise.

The safety valve is essentially an old-fashioned government price control that will curb the amount of private capital flowing to innovation and negate the market correction necessary to integrate economic growth with reductions in pollution. To accept a safety valve as part of a political compromise is to surrender the notion of legal limits on global warming pollution. No air pollution problem has ever been solved, anywhere in the world, without mandatory legal limits.

A real cap, a carbon tax, and a policy with a safety valve all increase the price of polluting as a way to discourage it. But similar means do not necessarily produce similar outcomes. The goal of climate change policy is not to send a price signal, but to reduce the quantity of global warming pollution so as to stabilize the climate.

Only a cap without loopholes delivers the scientific goods. The ultimate benefit of a true cap—in addition to a price signal that reduces emissions and pushes investment— is that it legally guarantees the cuts that science says we need. A policy with a safety valve falls short, as I have described. A tax simply cannot promise the necessary cuts—because, among other things, no one knows what level of tax will impact economic behavior enough to produce the necessary reductions in energy use and emissions. Global warming policies and carbon markets in the rest of the industrialized world are based on real limits, without loopholes. If the United States succumbs to a "best efforts" approach, without real accountability for an actual legal limit, we will undermine the possibility of an effective post-Kyoto agreement that ensures that all nations contribute the tons of emissions reductions necessary to solve this planetary problem.

Leaders in Washington might be open to an ineffective solution that is politically easier to swallow. I believe D. Kennedy underestimated the momentum, in and out of Washington, for a real solution to climate change. A year ago, pessimism would have been well founded. However, since then, a parade of interest groups and formerly skeptical legisla-

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tors have stood up in favor of a strong action.

Currently, 26 major companies have joined environmental groups in the U.S. Climate Action Partnership to lobby for an airtight cap on greenhouse gas emissions. House committee chairman John Dingell (D-MI), previously a skeptic, has promised an effective bill. In the Senate, the leader of the relevant committee is currently the author of one of the most aggressive bills to solve the problem. In the past month, the need for action was endorsed by the Business Roundtable, representing 150 companies, including Exxon Mobil. Four previously skeptical moderate and conservative senators—Lindsey Graham (R-SC), Blanche Lincoln (D-AR), Mary Landrieu (D-LA), and John Warner (R-VA)—came together to announce a new recommendation for reducing the cost of a cap on emissions without sacrificing the environmental goals. And 44 House Republicans broke ranks to support a resolution calling for serious, mandatory action to cut emissions.

Meaningful climate legislation is achievable in this Congress. As a principal voice of the scientific community, D. Kennedy and *Science* should insist on it. **FRED KRUPP**

Environmental Defense, New York, NY 10010, USA.

Climate Change: One Goal at a Time

LEGISLATION RECENTLY INTRODUCED BY Senators Bingaman, Specter, Harkin, Stevens, Murkowski, and Akaka, although not perfect, contains essential elements of a sound and durable climate policy for our nation. It would deliver mandatory, economy-wide reductions in all greenhouse gases; cover most emissions without a vast new bureaucracy; use trading to achieve maximum benefits at minimum cost; and generate substantial new funds to develop the technologies needed for a low-carbon future.

Some in the environmental community, however, are opposing the bill because it includes a "safety valve"—a price protection mechanism designed to ensure that the costs of reducing greenhouse gas emissions don't rise above a known, predetermined level. They view this feature as a fatal flaw. I couldn't disagree more.

Under Bingaman-Specter, there's no "escape hatch" from the financial consequences of emitting. Companies would buy additional allowances only if the costs of reducing emissions exceed a price threshold that starts at $12 per ton of carbon dioxide ($44 per ton of carbon) and escalates 5% above the rate of inflation every year thereafter. Many who oppose this provision also insist that cutting emissions will be relatively cheap. If they're right, the safety valve will never be used. But when it comes to designing a policy that calls this bet, confidence in low-cost solutions mysteriously evaporates.

I believe that those solutions do exist and that the cost cap in the Bingaman-Specter bill will be invoked rarely, if at all. But I also recognize that we are never going to pass a law unless we can convince legislators from heavily industrialized states that their concerns about U.S. jobs and competitiveness have been addressed. True, including the safety valve means opting—at least initially—for economic certainty over emissions certainty. But that's a trade-off worth making if it helps cut through the endless cost debates that have blocked action on climate change in this country for over a decade.

The safety valve is also important to guard against excessive price volatility in allowance markets. The potential for such volatility exists under a "hard" emissions cap, especially in the early years of program implementation. Nothing would erode support for a carbon cap-and-trade program more quickly than energy-price spikes caused by rapidly fluctuating allowance prices. Volatility serves no one's interests—except those of companies that profit by playing the market. It is no surprise, then, that business opposition to the safety valve is coming not from energy providers, but from financial traders and brokerage firms.

As the economy adjusts to carbon constraints, we'll need emissions certainty more than we need cost protection. The Bingaman-Specter bill provides the flexibility to adjust to changing circumstances by creating regular opportunities for Congress and the president to review and modify the safety valve and other program parameters. In the meantime, the safety valve plays a third crucial role: It invests the funds from allowance sales into technology incentives and R&D. The safety valve will only be triggered if our future technology options are poor, but it constantly hedges against that possibility by making deep investments in technology.

A key test for any climate policy is whether it changes the investment outlook for old-style coal-fired power plants. Any climate policy that keeps this option alive is not worth much. The Bingaman-Specter bill meets this test by providing new incentives for carbon capture and storage that, coupled with a price on carbon under the emissions trading program, will make advanced coal plants with carbon capture competitive with conventional technology.

Any law passed now must provide a strong starting point for long-term action. But further delay in pursuit of ideological purity doesn't advance the shared goals of the advocacy community or begin to provide answers for our rapidly warming planet. **HAL HARVEY**

William Flora Hewlett Foundation, Menlo Park, CA 94025, USA.

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 3 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

TECHNICAL COMMENT ABSTRACTS

Comment on "A Semi-Empirical Approach to Projecting Future Sea-Level Rise"

Simon Holgate, Svetlana Jevrejeva, Philip Woodworth, Simon Brewer

Rahmstorf (Reports, 19 January 2007, p. 368) presented an approach for predicting sea-level rise based on a proposed linear relation between global mean surface temperature and the rate of global mean sea-level change. We find no such linear relation. Although we agree that there is considerable uncertainty in the prediction of future sea-level rise, this approach does not meaningfully contribute to quantifying that uncertainty.

Full text at www.sciencemag.org/cgi/content/full/317/5846/1866b

Comment on "A Semi-Empirical Approach to Projecting Future Sea-Level Rise"

Torben Schmith, Søren Johansen, Peter Thejll

Rahmstorf (Reports, 19 January 2007, p. 368) used the observed relation between rates of change of global surface temperature and sea level to predict future sea-level rise. We revisit the application of the statistical methods used and show that estimation of the regression coefficient is not robust. Methods commonly used within econometrics may be more appropriate for the problem of projected sea-level rise.

Full text at www.sciencemag.org/cgi/content/full/317/5846/1866c

Response to Comments on "A Semi-Empirical Approach to Projecting Future Sea-Level Rise"

Stefan Rahmstorf

Additional analysis performed in response to Holgate *et al.* and Schmith *et al.* shows that the semi-empirical method for projecting future sea-level rise passes the test of predicting one half of the data set based on the other half. It further shows that the conclusions are robust with respect to choices of data binning, smoothing, and detrending.

Full text at www.sciencemag.org/cgi/content/full/317/5846/1866d

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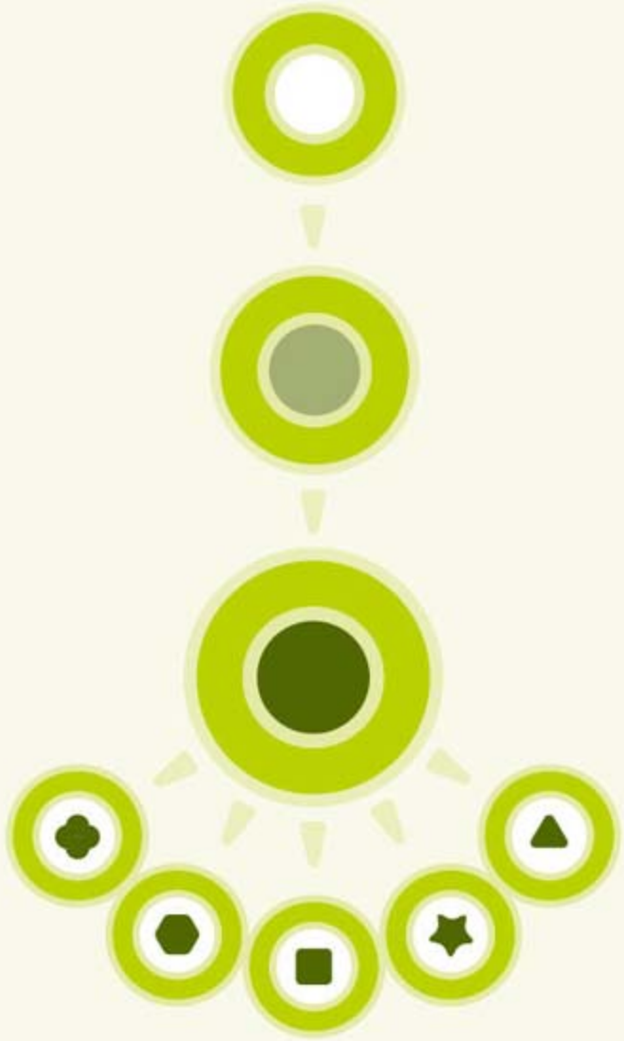

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HISTORY OF SCIENCE

Myths and Consequences

Michael Witzel

This book is about a long-gone, hypothetical people, the Indo-Europeans, who were once wrongly called "Aryans." We only know about them through their well-reconstructed language, which was spoken around 3000 BCE. Most languages of Europe, as well as Indo-Iranian languages (Persian, Sanskrit, Hindi) and the extinct Tocharian of western China, descend from it. However, *Aryan Idols*, originally published in Swedish seven years ago (*1*), deals only marginally with Indo-European linguistics. Rather, Stefan Arvidsson (a scholar of religion at the University of Halmstad) analyzes the misuse that Indo-European linguistics has been put to over the 200 years since its inception.

This misuse is intimately intertwined with convoluted history of the term "Aryan": *ārya* was the self-designation of the Iranians—Iran means "(the country) of the Aryans"—as well as of the ancient Vedic Indians, whose descendents now speak Indo-Aryan languages such as Hindi, Urdu, etc. However, during the 19th century Aryan was often used to designate all Indo-European languages and their speakers. From this the Nazi usage of Aryan was derived, in which it meant also the "race" of its speakers, particularly that of northern Europeans.

Unintended consequences of technical labeling and the misuse of the results of scholarship by nonspecialists are both ubiquitous and specific for particular periods. The history of "Aryan" ideas is that of a series of follies that, in some shape or form, still continue. They simply reflect the cultural history of Europe and America from the 1780s until today.

Aryan Idols
Indo-European Mythology as Ideology and Science

by Stefan Arvidsson

Translated from the Swedish (*1*) by Sonia Wichmann. University of Chicago Press, Chicago, 2006. 366 pp. $55, £35. ISBN 9780226028606.

The successful reconstruction of the Indo-European parent language in the early 19th century resonated well with the search for ultimate origins prominent at the time, resulting in fantasy-laden histories. The non–Indo-European Finns and Hungarians, too, searched widely for their homeland, in Tibet. Such inventions of tradition may appear only to be of historical interest now, but people are still fascinated by their origins and ancestors, as the current enthusiasm for DNA testing in genealogy shows. The Aryan folly continues with current chauvinist fantasies that influence one billion Indians now. In their own Aryan myth (not treated by Arvidsson), Aryans are the indigenous "sons of the soil" of their "fatherland," where they constitute "one country, one people, one culture." We have heard all of that before.

Martin Eskil Winge, Thor's Battle Against the Giants and the Midgård Serpent (1872). In the 19th and 20th centuries, this scene, "Apollo's struggle against Python, and Indra's fight with Vrtra were interpreted … as the struggle of the Aryan against both the brute force of nature and primitive peoples."

Arvidsson provides a detailed discussion of the twists and turns of the debate over the past two centuries, useful summaries, and some simplified tables that allow for quick orientation. He presents clearly the complicated web of mutual influences—for example, those spreading from Max Müller to Sylvain Lévi and from Lévi to Leopold von Schroeder. The latter was an important figure in the circle of the composer Richard Wagner and the racist Houston Chamberlain, whose ideas became influential in the development of Nazi concepts: intellectual *Glasperlenspiel* soon turned into real-life politics.

Unfortunately, Arvidsson usually relies on secondary sources. That approach is practical when dealing with 200 years, but it leads to some imbalances. Thus, the work of Franz Bopp, the actual founder of Indo-European linguistics, is mentioned only in the margin, and Arvidsson's description of Indology does not indicate the nature of the discipline well. Although he quotes many passages, thankfully in the original languages, the translations from German (via Swedish?) are not always correct (nor are individual references in the bibliography).

In sum, *Aryan Idols* is a useful analysis and summary, even if it is not always reliable or complete and occasionally is even a bit biased, as will be seen.

It is only possible to give a few highlights of the history of Indo-European Aryan myths. The relationship between Sanskrit and the other Indo-European languages was first elaborated in a Calcutta speech by William Jones in 1786 and in Bopp's grammar of 1816 (*2*). During the Romantic period, the pan-European search for origins led to imagining an Indo-European homeland in India, as Sanskrit was seen as the oldest form of Indo-European. The second half of the 19th century was dominated by the Oxford Indologist Max Müller and his Romantic interpretation of Vedic and Indo-European materials as primitive nature mythology, reshaped by the "disease of language." However, in the 1870s, when the strict neogrammarian school realized that Sanskrit was but a daughter of Indo-European, scholars started to look for another original Indo-European homeland.

Concurrently, during this period of European dominance, Darwinism and "race science" emerged and a new myth took form: a European or even Nordic Aryan race of noble warriors had conquered western and southern Eurasia. Some scholars, such as Müller and the linguist Hermann Hirt (neglected by

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Arvidsson), opposed any connection between language and race. Nonetheless, this new folly was combined with the nascent field of archaeology, fueling further fantasies about Indo-Europeans as Nordic agriculturalists, which resulted in the later Nazi "blood and soil" ideology. Mixing all of the above, amateur writers of the early 20th century such as Alfred Rosenberg laid the ground for Nazi ideology. Race studies and eugenics emerged as "sciences" in many countries. During the 12 years of Nazi reign in Germany, the heady Aryan brew had its most disastrous consequences in the extermination of "non-Aryans," including the Indo-Aryan Roma (Gypsies).

After 1945, other, still-current, interpretations of Indo-European myths and archaeology took over. Again, nonlinguists made wrong use of the results of one science to build theories for another. The Indo-European mythologist Georges Dumézil, the scholar of religion Mircea Eliade, and the archaeologist Marija Gimbutas predominated in the postwar period. The latter still is somewhat influential in tracing Indo-European horsemen's invasions out of the Ukrainian and Russian steppes into a supposedly peaceful, matriarchic Old Europe. The three have recently been accused of fascist tendencies, and Arvidsson even speculates that the Lithuanian-born Gimbutas's stance was due to her anti-Russian feelings. This kind of analysis may be fashionable (Foucault, Derrida); however, Arvidsson makes an art form of it—as when he even detects "catholic" (P. W. Schmidt, W. Koppers) and "protestant" writers on Indo-European myth. Throughout the book, we find such linkages between contemporary socioreligious developments and the development of Aryan fantasies.

Arvidsson's sympathies clearly are with Bruce Lincoln, who has recently turned a critic of certain Proto–Indo-European hypotheses, maintaining that the ancestral mythology of circa 3000 BCE cannot be reconstructed. But, as with the ancestral mythologies belonging to other language families, our understanding of it can be put on much firmer ground through combined historical and comparative methods (as I hope to demonstrate in a forthcoming book).

Arvidsson does see one way out of origin myths of the Aryan kind, through the comparative study of history. But he overlooks the recent internal critique made by Indo-European linguists, such as Stefan Zimmer (*3*), who have clearly pronounced against using "linguistic paleontology." Many others also distinguish between genuine linguistic discussion and gratuitous speculation that correlates linguistics with archaeology or, currently, with population genetics. Still, such methodological discussions do not deter some from creating ever new myths (e.g., the current Aryan one in India). Myth making and consumption seem to be permanent parts of the human search for origins. Arvidsson's way out of this conundrum is contravened as the writing of history gets increasingly hijacked by ideological, religious, and local nationalistic movements. What then?

Clearly, more serious historical and comparative scholarship is required. We also need the engagement of scholars willing to take public stands—whether in the battles over creationism or in the recent attempts by Hindu nationalists and fundamentalists (in both India and California) to rewrite Indian history in a mythological fashion (*4*). Aryan fantasies have indicated the inherent dangers most clearly, and here lies one of the enduring merits of Arvidsson's book: it indicates how we can actually learn from history.

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10.1126/science.1141619

EXHIBITION: ANTHROPOLOGY

The Disaster Business

katastrophē, from *katastrephein* to overturn, from *kata-* [down] + *strephein* to turn

Although the perpetual threat of disaster makes us fear the unexpected, our imaginations also prepare us to manage disorder and suffering. Consequently, given some period of peace after a catastrophe, societies rapidly regroup and act not only to assist their own members but also to help others, often far distant and quite anonymous, to rebuild their infrastructure and their faiths. The objects that help humans to be so resilient are the subject of the exhibition *Scénario Catastrophe*, curated by Christian Delécraz, Laurie Durussel, and Alessia Fondrini, currently at the Musée d'ethnographie de Genève. An accompanying volume offers essays from an interdisciplinary range of authors that includes anthropologists, artists, social psychologists, historians, agronomists, aid workers, and journalists.

Archetypal means of survival. A model of Noah's ark from Russia.

CREDIT: J. WATTS MUSÉE D'ETHNOGRAPHIE DE GENÈVE

The exhibition (in French and English) brings a multimedia perspective to coping with disaster. At the start, visitors are surrounded by the sounds of doom: war, earthquake, klaxons, radio announcements, and wailing children. They are then safely delivered into a suburban sitting room where the television chatters an amiable counterpoint. Hanging on the walls and shelves of the room are a selection of fetish objects.

People take a variety of approaches to satisfy their desire for advanced warning of impending catastrophe. In most societies, amulets commonly feature animals. The primary explanation is that many animals are sensitive to and alarmed by subtle environmental signals that precede extreme weather, fire, avalanche, and earthquakes. An example that deviates from the more-expected selection of birds, elephants, and cows was the red spiny oyster, *Spondylus princeps*. This mollusc had originally been adopted as a votive object by pre-Columbian people: oyster shells washed up on the western shore of South America presage El Niño inundations, as this species tends to die en masse if the seawater temperature rises.

Despite the continuing importance of folk amulets, societies have increasingly favored a technical quest for an ideal security through recent developments in seismographs, avalanche and tsunami detectors, meteorological forecasting, and so on. Not withstanding the impressive technology available, we still have a largely illusory mastery over the natural world.

One part of the exhibition considers commemoration as a vital aspect of societal repair. With specific commemorative objects and commemoration events, past disasters can be categorized and psychologically

contained while societies rebuild and attempt to return to a sense of normality and security. Clocks make potent symbols of the delicate machinery of the human body, and the stopped clock has been adopted as a particularly haunting commemorative object. The interrupted hour has been frequently depicted in remnants of clocks such as those surviving the San Francisco earthquake of 18 April 1906 (05:14); the Hiroshima nuclear bomb blast of 6 August 1945 (08:15); and the passage of Hurricane Katrina on 30 August 2005 (02:02 to 14:30).

The exhibition reminds us how important religion is as a survival aid and as a means of keeping societies intact and functioning in the common interest when assaulted by disaster. Religious objects serve as enduring tools for emotional survival and for warding off further danger; for some catastrophes (especially those caused by humans) such fetishes may ultimately be more effective than a spade or a gas mask. Apart from pleading for intercession with the gods via guardian angels and portable oratories, acts of donation can be construed as offerings. Nevertheless, as the exhibition points out, the occasionally extreme levels of generosity raise disturbing issues themselves. How should the money be used in a considerate and effective way? How do we explain the global nature of the emotional response to some disasters, such as the Indonesian tsunami, and the relative silence surrounding others, such as the unfolding events in Darfur? We don't find answers in this exhibition, but we are forced to question our responses to remote human disasters.

The exhibition considers many, often conflicting, attributes of coping. Quite clearly, disaster is not a calamity for everyone. The specter of doom has always been exploited politically as a means of gaining power and keeping control. The curators offer the U.S. Patriot Act of 26 October 2001 as an example of how a modern democracy can persuade people of the importance of abandoning some of their civil liberties. The neologism "libertiicide" is a provoking exhibit in itself. Purportedly operating as vehicles for public information, the media are adept at amplifying anxiety and manipulating the general public's perception of risk. Here, the exhibition invites us to consider society's response to stories about avian influenza and the millennium bug. In 2005, the British government aimed to buy a stockpile of 14.6 million courses of the antiviral drug Tamiflu, and over 600 million U.S. dollars were spent between 1995 and 2000 in attempts to avert an anticipated computer systems meltdown as the millennium arrived. This human tendency to imagine the worst also prompted Henri Dunant (the Swiss founder of the Red Cross movement), in his later years, to illustrate his vision of the end of the world in a complex painting displayed at eye level in all its frightening detail.

Scénario Catastrophe

Christian Delécraz, Laurie Durussel, and Alessia Fondrini, curators

Musée d'Ethnographie, Genève, Switzerland, through 6 January 2008. www.ville-ge.ch/musinfo/ethg/expo06_uk.php

Scénario Catastrophe

Christian Delécraz and Laurie Durussel, Eds.

Infolio, Gollion, Switzerland, 2007. 352 pp. Paper. CHF 16, €11. ISBN 9780521858915.

Disaster can also be good for business. In 1989, 300 people lived in the town of Lokichokio in Northen Kenya. War in Southern Sudan brought to the town 25,000 aid workers, who had needs of their own. The influx in turn spawned numerous small businesses, few of which survived when the war moved away and the aid workers transferred their operating center. The disaster business has now expanded into a huge global enterprise trading in the tools of survival. The scale of the business has led to dedicated trade shows, which feature specialized spades, bulldozers, infrared detectors, earthquake monitors, and what have you. "Aid and Trade" is held annually in Geneva, capitalizing on the city's location as a hub for the international organizations that focus on disaster management.

If catastrophe makes people question the natural order, it can provide other opportunities—opportunities to reform society, for instance. A notable example is the so-called Lisbon earthquake of 1 November 1755, which in fact affected much of the Iberian Peninsula and the northern tip of Africa. The resulting destruction prompted the de facto head of the Portuguese government, the Marquis de Pombal, to conduct an enquiry to find a rational explanation for the disaster that was free of Jesuit influence and divination. He thereby triggered a surge of geological investigations across Europe and allowed the fresh air of Enlightenment thinking into the Portuguese backwater.

Superstition still prevails when it comes to prediction, warning, and prevention. Nevertheless, apocalyptic visions help us to prepare for future catastrophes. The final section of the exhibition is devoted to contemporary human views of disasters yet to come. End-of-time stories once told in the smoky firelight might have been replaced by bright electronic media, but the monsters, tsunamis, and earthquakes as well as the fear, damage, and ultimately death can still be found in contemporary stories.

Scénario Catastrophe is the best kind of museum exhibit—maybe no answers, and maybe some confusion, but in every way surprising and provocative. Although the presentation is intended to be objective and neutral, the impression we are left with is compassionate and positive: a sense that humans will always work together to repair broken societies. But we know this is not always the case. What happens when catastrophe leaves the surviving people so traumatized they are not able to rebuild a functioning society? Or what about cases when the society that is rebuilt is dysfunctional, causing further harm and trauma to its members?

–Caroline Ash

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BROWSING

The Telescope. Its History, Technology, and Future. Geoff Andersen. Princeton University Press, Princeton, NJ, 2007. 256 pp. $29.95, £18.95. ISBN 9780691129792.

As we approach the 400th anniversary of Hans Lippershay's 1608 patent for a refractor telescope, Andersen offers an accessible, nontechnical account of instruments that show us distant objects. He begins with the naked-eye view of the universe and a rapid survey of new designs, theories of light, and astronomical findings from Galileo, Huygens, Newton, and others. But he soon abandons the chronological narrative to address various topics. A series of chapters covers the basics of telescope design, optics, instruments for analyzing light, and even considerations for building one's own observatory. There are short but informative discussions of interferometry and advanced telescope techniques (segmented mirrors, the use of computers to counter the distortion of images by atmospheric turbulence, etc.). The author's research experiences probably explain his decision to present applications of telescopes to remote sensing, laser communications, and surveillance. Given the flavor of the book, the short and idiosyncratic list of "key discoveries" could have been sacrificed to provide expanded treatment of unconventional and future telescopes.

RELEVANCE

Pharmacology in the High-School Classroom

Making learning relevant improves students' knowledge of biology and chemistry.

Nicole C. Kwiek,[1]* Myra J. Halpin,[2] Jerome P. Reiter,[3] Leanne A. Hoeffler,[1] Rochelle D. Schwartz-Bloom[1]†

Many teachers say that their most difficult task is getting students' attention. What does get students' attention? Sex, drugs, and rock-n-roll, of course.

U.S. high-school students rank relatively low in science achievement compared with their international peers (*1*). Factors that may contribute to poor science achievement include (but are not limited to) inadequate teacher training, lack of inquiry-based teaching, insufficient hands-on student activities, and students' views of science as boring or too hard (*2*, *3*). A positive relation exists between student interest and student learning: Topics and approaches that arouse student interest can help motivate students to learn and increase achievement (*4*). Theories of constructivism (that learners formulate new understandings by building on their own prior ideas) from cognitive psychology also indicate that learning improves when information is embedded within meaningful contexts (*5*).

When high-school students are asked to indicate their interest in learning about various topics in their science classes, they choose topics such as disease (cancer and HIV/AIDS), drugs (therapeutic and recreational), biological and chemical weapons, the ozone layer, and greenhouse gases (*6*). Yet, the usual high-school science curriculum does not address these topics.

Pharmacology Education Partnership

Given the interest of students in drugs and their bodies, we hypothesized that science instruction in the context of drug-related topics (i.e., pharmacology) could improve student learning of standard high-school biology and chemistry concepts. To study this issue, we developed the Pharmacology Education Partnership (PEP), a partnership between Duke University faculty and high-school teachers across the United States. The PEP project comprised three major components: (i) development of pharmacology content modules, (ii) professional development for teachers of high-school biology and chemistry, and (iii) assessment of students' knowledge of basic biology and chemistry concepts.

Each pharmacology module was designed in an inquiry-based format. Details of the contents of the module and the teachers' guide are found in the supporting online material (SOM) and on the PEP Web site (*7*). The modules focused on a pharmacological topic that integrated basic science principles in biology and chemistry with issues from other relevant disciplines such as mathematics, public policy, psychology, and social sciences. Topics (see figure, right) were chosen with an expectation that students would identify with the subject matter on the basis of personal experience or interest generated from popular culture and the media.

High-school biology and chemistry teachers were recruited nationally to take part in the PEP study (see demographics in SOM). The process began when 116 teachers attended day-long professional development workshops at one of three conferences, including the Conference on Science Education for the National Science Teachers Association (NSTA) and the North Carolina Science Teachers Association (NCSTA) in 2003 (SOM). The workshops showed how biology and chemistry concepts support the pharmacology topics in the modules. Teachers discussed how to bring these topics into their already crowded curriculum. After the workshop, teachers collaborated to develop classroom and laboratory activities to support each module (activities are available on the PEP Web site). Assessment of teacher knowledge one year after the workshops indicated gains in knowledge of biology and chemistry (SOM).

The following year after the workshops, 95 of those teachers field-tested the program in their classes (21 teachers dropped out during the year for unknown reasons). Because teachers often modify use of instructional materials according to their own style (*8*), we invited that flexibility; we requested only that teachers use as many modules as possible and report what they did. Of the teachers who used modules in their classes, the most commonly reported method was to incorporate the content in their normal lesson plans, without "piling on additional material" (SOM). The most commonly reported reason for not using the modules was lack of time (SOM), suggesting that priority was given to preexisting curricula.

MODULE TOPICS

- Acids, Bases, and Cocaine Addicts
- Drug Testing: A Hair-Brained Idea
- How Drugs Kill Neurons: It's Radical!
- Military Pharmacology: It Takes Nerves
- Why Do Plants Make Drugs for Humans?
- Steroids and Athletes: Genes Work Overtime

Student Assessment

With input from an advisory group of five high-school teachers (independent of our testing group), we developed a testing instrument to determine students' knowledge of standards-based biology and chemistry concepts. The test consisted of two parts (see SOM for sample questions). The "basic knowledge" questions were similar to those found in standard high-school biology and chemistry textbooks. The "advanced knowledge" questions tested specifically for knowledge about drugs, assessing concepts not normally taught in the standard curriculum. To obtain control data, 65 of the 95 teachers had the workshop soon enough that they were able to administer the tests to a separate group of students in the year before they used (field-

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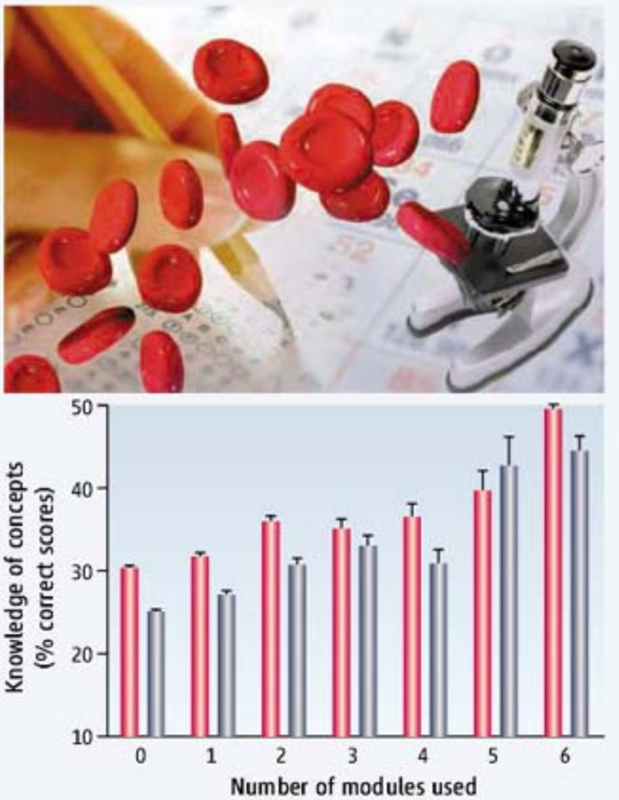
tested) the modules as a teaching component. The other 30 teachers joined the study later and thus did not generate control data.

During the field-testing year, 47 of the 95 teachers used the modules in their classes. Then, all 95 teachers administered the same test (unannounced) to their students. Although the control data were derived from different students than those who used the modules, the demographic profiles were the same. A total of 7210 students provided data for the study. Student achievement demonstrated a dose-response relation: As the number of modules experienced increased, the students' performance increased (see figure, right).



Student improvement with exposure to modules. Performance of all students on questions of basic (red) and advanced (blue) knowledge depending on the number of PEP modules they experienced. Data are the mean ± SEM scores from students in both biology and chemistry courses (n = 7210). Binomial regression revealed that the use of at least one module was a significant predictor of higher student scores for both tests.

We used a logistic regression model to adjust for differences in students' demographic characteristics (gender, race/ethnicity, course type, and level) with the use of random effects to control for teacher effects (*9*, *10*) (SOM). For both basic and advanced knowledge questions, the logistic regression indicates that the probability of students answering any question correctly increases significantly as teachers use more modules (SOM). Students exposed to all six different modules are more likely than students with zero exposure to answer a basic knowledge question correctly. This corresponds to about a 16–percentage point increase (compared with zero modules) in the chance of a white female in Biology One (the baseline, SOM) answering correctly. When our analysis includes only the students from the 65 teachers who served as their own controls, the modules still have significant positive effects, providing assurance that the module effects are not likely confounded by teacher and student effects (e.g., only the best teachers used the modules).

Relevance, Repetition, Integration

The PEP topics such as drugs of abuse and chemical warfare carry personal, societal, and global relevance, which may have supported the successful outcome of this educational intervention. Similar attention to the students' interests may improve effectiveness of science education reform initiatives in other disciplines as well. Alternatively, consistent with educational research findings, the student-learning gains may have been strengthened by repetition of important principles among modules (*11*). Although we cannot state with certainty whether the use of socially relevant topics or repetition of scientific principles is responsible for the educational gains, at the very least the pharmacology topics can support repetition without boring students.

The teacher-training workshops, crucial to this program, fulfilled several elements of the National Science Education Standards (*12*). In particular, the teachers learned new information (in this case, basic pharmacology principles) into which they could integrate biology and chemistry concepts. This sort of cross-connective experience is rare for secondary school teachers (*13*). Although we did not test for the effect of integrating disciplines on student achievement, the pharmacology topics supported improved student performance in both biology and chemistry. Such integration across science disciplines is a proposed goal of science education reform efforts (*14*).

Reproducibility

Our results for both teacher and student content knowledge are similar to another study in which we provided the professional development over 5 days at Duke University and used a wait-listed randomized control design (*15*). The 6-hour workshop content was the same as that provided in the present study, although teachers had some "hands-on" time and interactions in small groups during the longer format. Regardless, both forms of professional development are associated with a significant increase in student achievement in biology and chemistry. From a practical standpoint, a full-day professional development experience is efficient and cost-friendly; its design allows more teachers to participate (compared with a residential 5-day workshop), eventually affecting a much larger student population.

A prevailing goal of science education is to encourage students to use science to think critically when making decisions about their daily lives (*2*). Although preventing drug abuse was not a goal of the present study, more knowledge about street drug pharmacology may help students make better decisions concerning illicit drugs.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/317/5846/1871/DC1

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ANTHROPOLOGY

Tracking Polynesian Seafarers

Trace element and isotope analysis of basalt adzes demonstrates long-distance voyaging paths used in East Polynesia long before European arrival.

Ben Finney

About 4000 years ago, Stone Age voyagers from Island Southeast Asia began to sail east into the Pacific, where they settled the previously uninhabited islands of Remote Oceania (Eastern Melanesia, Micronesia, and Polynesia). As Europeans began exploring the Pacific, they were surprised to find that mid-ocean islands were occupied by seemingly primitive seafarers, who had only slim canoes carved with stone adzes, powered by mat sails, and navigated without instruments. Some Europeans could not accept that such seemingly ill-equipped people had settled the islands on their own. They instead imagined such scenarios as storms or currents pushing coastal people far out to sea, the sinking of a great continent leaving only high peaks and surviving inhabitants above water, and the special creation of humans on the islands.

A few prehistorians still begrudge the Remote Oceanians only minimal seafaring skills, but more than two centuries of research have led to widespread appreciation of their nautical capabilities. On page 1907 of this issue, Collerson and Weisler (*1*) confirm the wide extent of Polynesian voyaging by chemically tracing basalt adzes found on coral atolls to specific volcanic sources.

Not until the late 1700s did foreign explorers consider seriously how canoe people could have actively settled the Pacific. Captain Cook and Joseph Banks judged Tahitian sailing canoes and navigation methods fit for long voyages. By comparing Tahitian words with those gathered from islands far to the west, they realized that Tahitian was related to languages of the "East Indias." Upon hearing from the Tahitian savant Tupaia how navigators waited for seasonal spells of westerly winds to sail east against the trade wind direction, Cook presciently suggested that their ancestors had used these westerlies to sail east into the ocean (*2*).

During the 1800s, amateur scholars collected oral Polynesian migration traditions. The histories they produced were highly suspect, because they cut and pasted together passages from various narratives and committed other scholarly sins. Nonetheless, the unedited traditions, and increasingly sophisticated linguistic comparisons, suggested migration paths.

During the past century, ethnologists and archaeologists sought to trace these paths by comparing artifacts from various islands, but with mixed results. Canoe comparisons became mired in turgid debates over canoe typology, outrigger attachments, and migration waves. Stylistic comparisons of temples, adzes, and fishhooks fared better, but often foundered over whether features from different islands were similar because of a common origin or convergent adaptation.

The breakthrough came in the 1960s and 1970s, when the discovery of distinctively decorated Lapita pottery enabled archaeologists to track the rapid entry of the Polynesians' ancestors into Remote Oceania. The many potsherds proved ideal for stylistic comparisons, and in some cases, geologists were able to source constituent temper sands to islands near and far. The wide range of Lapita voyaging was demonstrated even more dramatically by chemically tracing obsidian tools to volcanic sources scattered over hundreds and in some cases thousands of kilometers of the Western Pacific (*3*).

At about the same time, other researchers were reconstructing extinct Polynesian voyaging canoes and testing them over legendary long-distance sailing routes (see the figure) (*4*), studying traditional navigation on remote Micronesian and Melanesian islands where voyaging had not died out (*5*), and using computer simulations to elucidate strategies of ocean exploration and island colonization (*6*). These efforts supported the hypothesis that Remote Oceanians were capable of purposefully making long navigated voyages and settling distant islands.

Unfortunately, pottery making declined after Lapita voyagers reached the mid-Pacific, and was not spread farther east by their Polynesian descendants. Moreover, although obsidian occurs in New Zealand and Easter Island, tools made from this type of volcanic glass were apparently not widely spread from these peripheral islands.

In the 1980s and 1990s, archaeologists therefore turned again to stone adzes, particularly those made from fine-grained oceanic basalts of the "hot-spot archipelagos" of East Polynesia. This time they used major-element composition to trace each piece of basalt back to its geological source. This approach allowed intra- and interarchipelago connections to be traced over much of Polynesia, but did not always allow the precise sources of the basalts to be identified (*7*).

To more precisely source basalt adzes collected over 70 years ago among East Polynesia's Tuamotu atolls, Collerson and Weisler turned to more discriminating analyses possible with trace elements and isotopes. The results indicate that the adzes came from five volcanic archipelagoes surrounding the Tuamotus, and to particular islands within these, such as Hawai'i's Kaho'olawe (some 4000 km to the north-northwest). The authors do not hesitate to relate this connection to legends of canoe voyaging between Hawai'i and Tahiti via the Tuamotus, as well as the 1976 voyage over this route of the modern double canoe *Hokule'a* (see the figure) (*8*).

Sailing *Hokule'a* from Hawai'i to Tahiti via the Tuamotus in 1976.

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Consilience (*9*) between disparate research approaches works well in Polynesia (*10*). Further integration of chemical sourcing with other approaches, especially DNA investigations of Pacific islanders and their plants and animals, looks promising. For example, a bone of a Polynesian chicken excavated in Chile has recently provided archaeological support for Polynesians having reached South America in pre-Columbian times (*11*). Now we need to look for Polynesian basalt adzes there.

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PHYSICS

Quantum Weirdness in the Lab

The surprising effects of adding or subtracting photons from a light beam may yield tools for information processing.

Robert W. Boyd, Kam Wai Clifford Chan, Malcolm N. O'Sullivan

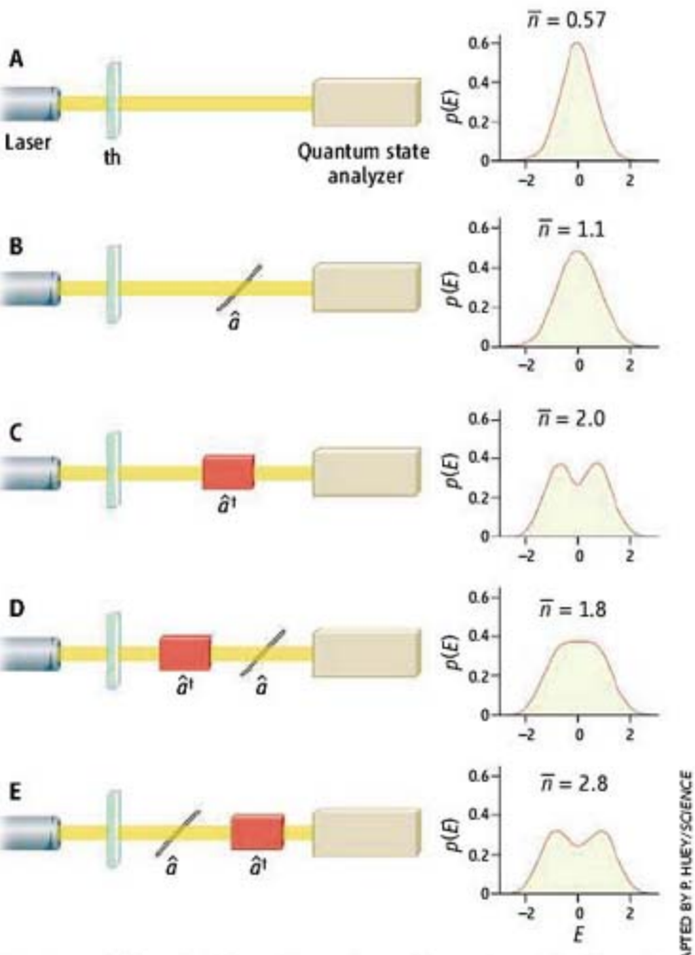
In ordinary arithmetic, multiplication obeys a commutative law. That is, for any two numbers n and m, the product nm is always equal to mn. In classical physics, measurements of physical properties also obey a commutative law. For example, if one first measures the position of a particle and then its momentum, one obtains the same result by first measuring the particle's momentum and then its position. However, quantum mechanical quantities do not in general obey this commutation relation (*1*). In fact, the breakdown of the commutative law lies at the heart of many fundamental quantum properties, such as the Heisenberg uncertainty principle. In the example of position and momentum, the lack of commutativity is conventionally stated by means of the relation $\hat{x}\hat{p} - \hat{p}\hat{x} = ih/2\pi$, where $\hat{x}$ and $\hat{p}$ are the quantum mechanical operators (*2*) associated with position and momentum, respectively, and where h is Planck's constant.

In an intriguing and illustrative report on page 1890 of this issue, Parigi *et al.* (*3*) present the results of a laboratory demonstration of what happens in the quantum mechanical operations of photon creation and annihilation, which lacks commutativity. These authors add a single photon to a light beam, which corresponds to the action of the standard quantum mechanical creation operator $\hat{a}^\dagger$. They can also subtract a single photon from the light beam, which corresponds to the annihilation operator $\hat{a}$.

Parigi *et al.* measure the quantum mechanical state of a thermal light field after performing these two operations on it, and they show that the final state depends on the order in which the operations are performed. This result is a striking confirmation of the lack of commutativity of quantum mechanical operators. Moreover, the authors present the strongly counterintuitive result that, under certain conditions, the removal of a photon from a light field can lead to an increase in the mean number of photons in that light field, as predicted earlier (*4*).

The basic idea of the experiment of Parigi *et al.* and some of their results are shown in the figure. In the top row, a laser beam passes through a rotating ground glass plate (th) to mimic the random fluctuations of a thermal source and is detected by a quantum state analyzer (QSA). The results of the measurement are shown on the right. Here, $p(E)$ gives the probability distribution of the electric field amplitude E. Rows B through E illustrate the consequences of acting on the input state by various quantum mechanical operations. Row B shows the result of removing a single photon from the field with a beam splitter. Counterintuitively, the mean number of photons $\bar{n}$ in the output field is increased by this operation. Row C illustrates the consequence of adding a single photon to the input state with an optical parametric amplifier (a device that splits one photon into two, each with approximately half the energy of the original photon). Row D illustrates the consequence of first adding a photon to the field and then subtracting a photon, whereas row E illustrates the situation in which a photon is first subtracted and then a photon is added. One sees that the fields created in these two situations are markedly different.

Beyond the conceptual interest in the



Quantum arithmetic. Schematic experimental procedure of Parigi *et al.* and some of their laboratory results. The order in which photons are added and subtracted from a light field strongly influences the field's properties.

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results of Parigi *et al.*, the laboratory techniques they describe could pave the way toward new possibilities in the fields of quantum information science and quantum optics (*5*–*8*). These results show how one can convert a purely thermal light field, which possesses no nonclassical properties, into a light field with strongly nonclassical features. This work thus constitutes a step toward the development of techniques for "quantum state engineering," that is, the creation of states with specified quantum properties. States of this sort are expected to play a key role in quantum computing, quantum cryptography, and control of quantum systems.

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GENOMICS

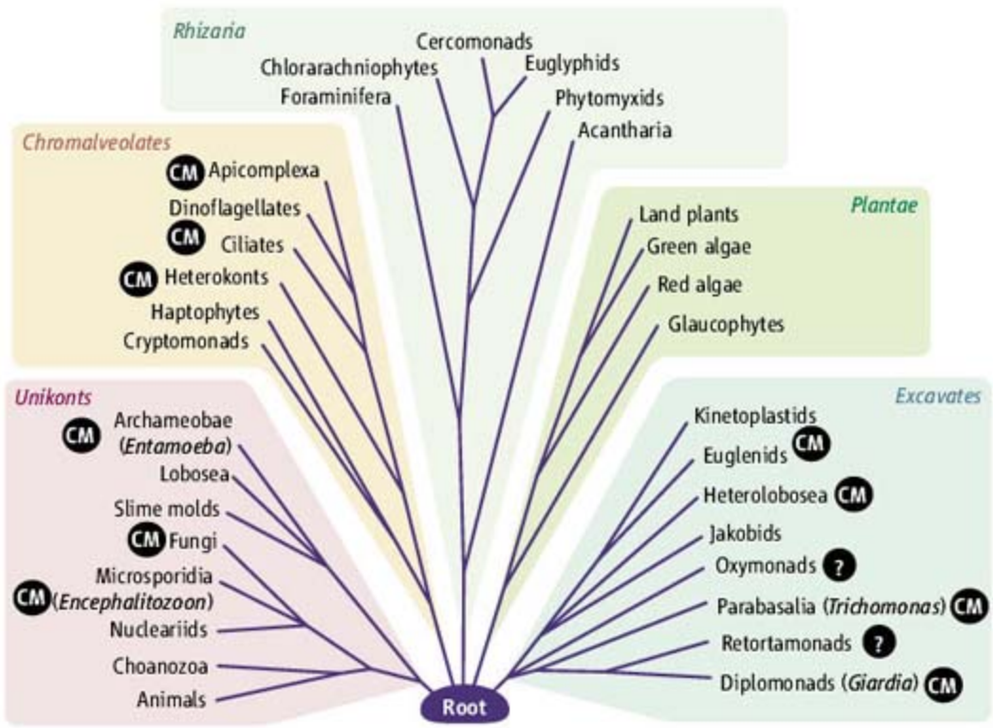
Deep Questions in the Tree of Life

Now that the genome of a unicellular parasite has been deduced, can it resolve the debate on the origin of eukaryotes?

Patrick J. Keeling

A genome sequence might provide answers to major questions about the biology and evolutionary history of an organism. Alternatively, it might reveal more problems than solutions, and its true value then lies in identifying what questions to ask. Perhaps the most interesting genomes do both: They are a panacea and a Pandora's box. On page 1921 in this issue, Morrison *et al.* (*1*) describe such a genome from the diplomonad protist *Giardia lamblia*, a human intestinal parasite. The compact *Giardia* genome is replete with information ranging from the simplicity of its molecular systems to how the parasite interacts with its environment. However, the evolutionary history of *Giardia* is not so clearly written in the genome, reigniting a smoldering debate about the origin of *Giardia* and its relationship to other eukaryotes.

The evolution of *Giardia* has commanded a level of attention matched by few other organisms because it differs from the "textbook" eukaryote in many ways. Most notably, there are no mitochondria in *Giardia* or its relatives, in keeping with its tolerance for low levels of oxygen (*2*). The absence of this organelle took on new significance with the Archezoa hypothesis, which proposed that *Giardia* (and certain other protists) diverged from other eukaryotes before the endosymbiotic origin of mitochondria, and was therefore ancient and primitively amitochondriate (*3*). Early molecular phylogenies supported this view, placing *Giardia* and other Archezoa at the base of eukaryotic evolution (*4*, *5*). The case seemed closed: *Giardia* arose from the prokaryote-eukaryote transition, one of the greatest transformations in evolution.



Eukaryotic evolution. The hypothetical evoultionary tree consists of five "supergroups" based on several kinds of evidence (*15*). The branching order of supergroups is unresolved, implying that the relationships are unknown rather than a simultaneous radiation. CM indicates the presence of cryptic mitochondria (hydrogenosomes or mitosomes). A question mark indicates that no organelle has yet been found.

The Archezoa hypothesis proved too good to be true. Nuclear genes phylogenetically related to mitochondrial homologs were discovered in Archezoa, including *Giardia* (*4*, *5*). The protein products of such genes have been localized to double membrane–bounded organelles (hydrogenosomes or mitosomes) in all major Archezoan groups, and similar structures were found in distantly related eukaryotes (see the figure). Some of these organelles and their metabolic activities are well characterized (e.g., *Trichomonas* hydrogenosomes), but the functions of other cryptic organelles remain elusive (e.g., *Entamoeba* mitosomes). In *Giardia*, proteins involved in iron-sulfur cluster assembly and protein folding appear closely related to mitochondrial homologs and localize to a relict mitosome (*6*, *7*). Interestingly, the *Giardia* genome contains little else of identifiable mitochondrial ancestry: No other functions can be predicted and protein-import complexes are reduced or highly divergent (*1*, *8*).

The other implication of the Archezoa hypothesis—that *Giardia* is an early branching eukaryote—has attracted even more controversy. The "deep" position of some Archezoa has been convincingly undermined

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by showing that they belong elsewhere in the phylogenetic tree, the clearest case being the relationship between microsporidia and fungi (*5*). For *Giardia*, such a specific alternative is not so clear-cut, but the genome may provide clues. Diplomonads may belong to a group of protists known as excavates, specifically related to Parabasalia such as *Trichomonas* (*9*, *10*). Like *Trichomonas*, the *Giardia* genome does not encode myosin (which is rarely absent from eukaryotic genomes) and encodes a bacterial arginine metabolism pathway, supporting a close relationship. This does not preclude an early divergence for both *Giardia* and parabasalids, for this depends on where the root of the eukaryotic tree lies, which is difficult to resolve. Indeed, there are doubts about how phylogenetic reconstruction methods can determine this root, given the unequal rates of sequence evolution and great genetic distance between eukaryotes and prokaryotes (*11*). There are also difficulties inherent in reconstructing the history of divergent genes with current phylogenetic methods, and large amounts of data that violate evolutionary models can generate well-supported errors (*12*). Morrison *et al.* show high levels of divergence in much of the *Giardia* genome, so although the genome may contain data to reconstruct *Giardia*'s history, it will be a challenge to use it.

The outcome of this debate affects not only our understanding of early eukaryotic evolution, but also our view of *Giardia* biology. Simple characteristics could be primitive or derived via reduction, alternatives with very different meanings. The simplicity of *Giardia*'s molecular systems differs from that of known derived parasites (*1*, *13*). However, different lineages can follow different reductive paths (*14*), so determining *Giardia*'s origins independently of its simplicity is essential. Given the depth of these questions, the new life that Morrison *et al.* have breathed into the debates is welcome, and will ensure continued attention on both a fascinating cell and the origin of eukaryotes.

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PHYSICS

Does Our Universe Allow for Robust Quantum Computation?

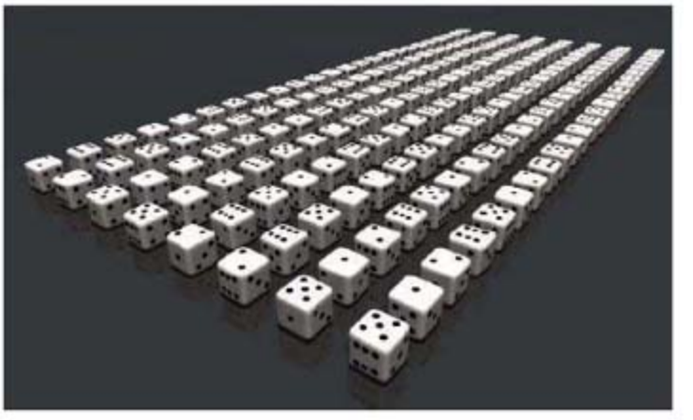
An approach for analyzing quantum decoherence may help push the boundaries of quantum computing.

Dave Bacon

Computers operating purely according to the laws of quantum theory might break modern cryptographic codes (*1*), revolutionize quantum chemical calculations (*2*), and overturn the most basic limits to computing (*3*). Standing in the way of creating these dream machines is the fact that quantum computers do not like to maintain their quantum nature, but instead have a propensity to decay into machines obeying the classical laws of physics. This obstacle is known as quantum decoherence, and on page 1893 of this issue, Emerson *et al.* (*4*) report a way to analyze various quantum processes to find the ones that can stand up to this decay.

The solution to the problem of quantum decoherence, at least in theory, has been known for more than a decade and is encoded in a famous theorem for fault-tolerant quantum computation (*5*–*8*). This "threshold" theorem says that multiple quantum systems can be used to simulate a single error-free quantum system. Left out, however, is the question of whether the theorem actually holds in an experimental setting: Does our universe allow for robust quantum computation?

This is a hard question because the cost (the number of experiments needed) of characterizing the properties of quantum systems useful for fault-tolerant computation rises exponentially with the number of quantum systems (*9*, *10*). Emerson *et al.* have found a way to probe quantum processes that has a cost that, contrariwise, scales polynomially in the number of quantum systems (that is, a much lower cost per quantum system). Although this method throws away a certain amount of information, it also retains much of the relevant information. Thus, the authors have opened the door on a new era where quantum devices can be rapidly characterized as useful or not useful for the task of building



Quantum casino. Emerson *et al.* propose a new scheme in which the evolution of a quantum system is symmetrized to eliminate unwanted information. The operations for a single qubit are shown as transforms of a gambling die. All 192 such operations on a die are displayed, 24 rotations and eight reflections of a die through a plane (which are impossible in our world and why you won't find those dice on a casino table). The procedure of Emerson *et al.* can be thought of as randomly selecting one die for each quantum bit in the system from the 192 choices and then applying the transform corresponding to that die to a corresponding quantum bit.

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a large-scale quantum computer.

To understand the problem addressed by Emerson *et al.*, it is convenient to consider a classical analogy. Suppose that you are the operator of a casino that runs a game using six-sided dice. Vital to your gambling business is verifying that the dice are balanced. By throwing a die multiple times, you can estimate the probabilities of each of the six different outcomes. For well-balanced dice, these probabilities will all be around 1/6, but for loaded dice, these probabilities may be drastically skewed away from 1/6. By measuring these six probabilities, you have in essence characterized the process of rolling a die.

You're a casino operator, however, and so you are extremely paranoid that your game of chance can be beaten. In particular, consider a game like craps where you roll two dice. What assurance do you have that these dice actually behave independently and thus have probabilities for outcomes A and B that are a product of the probability of outcome A times the probability of outcome B? You might tell your testers to run experiments where two dice are rolled together. Each die has six different outcomes, so there are a total of 36 different outcomes for a roll of these two dice. Thus, your testers will now need to run experiments to characterize 36 different probabilities. And here is the crux of the problem for characterizing the process of rolling dice. If you want to assure yourself that there are no correlations among n total dice, you will need to characterize 6^n different probabilities. Thus, the cost of your paranoia is an exponentially increasing expense you must pay your testers to measure each of the 6^n probabilities.

In many games, however, there is an assumption that greatly reduces the costs of testing multiple dice. Suppose that for your purposes, only the total sum of dots on n dice matters. For n dice, the total of the dice is a number between n and $6n$. Thus, if your testers record the probability of a given total of the dice, only $5n + 1$ probabilities need to be recorded. Instead of requiring a number of probabilities that scales exponentially in n, you only require a number of probabilities that scales polynomially (linearly in this case) with n. If, after you rolled your dice, you had randomly changed your dice such that the total stayed the same, this would not affect your measured probabilities. At the same time, information tied to properties besides the total is averaged away. With this process of "symmetrizing," you can eliminate unwanted information and only look at the much smaller subset of more relevant information.

What Emerson *et al.* have achieved is similar but for quantum systems. The laboratory technique of characterizing the time evolution of a quantum system is known as quantum process tomography (*9*, *10*). For n two-level quantum systems, this method requires approximately 2^{4n} experiments to characterize a quantum process. Emerson *et al.* have proposed a new technique that, by symmetrizing the quantum process, reduces this to a polynomial in n (see the figure). As in the dice example, this process discards information about the process being studied, but Emerson *et al.* point out that their technique can be used to test some of the main assumptions (such as whether the errors are independent) of the threshold theorem for fault-tolerant quantum computation.

As more devices are fabricated in which quantum theory dominates, accurate understanding of quantum processes becomes vital. The quantum process tomography techniques described here represent a first step toward accurately assessing the powers and limits of these new quantum machines. Indeed, thanks to the techniques developed by Emerson *et al.*, we may soon know whether our universe is generous enough to allow for large-scale robust quantum computation.

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ECOLOGY

Antarctic Biodiversity

Peter Convey and Mark I. Stevens

Forms of plant and animal life can be found across Antarctica that have survived glacial cycles over millions of years.

Only about 0.3% of Antarctica is free of ice. The terrestrial and freshwater ecosystems in this tiny fraction are generally small and isolated, and are populated by small invertebrates, lower plants, and microbes (see the figure). Recent studies have shown that these biota are of ancient origin and have persisted in isolation for tens of millions of years. However, ice sheet modeling of the Last Glacial Maximum (~20,000 years ago) and previous ice maxima in the Miocene (23 to 5 million years ago), along with reconstructions of previous glacial extent, suggest that most or all currently ice-free low-altitude surfaces would have been covered with ice during previous glacial maxima (*1*, *2*). These models leave no ice-free refuges for most terrestrial biota, and they require recolonization after each glacial maximum.

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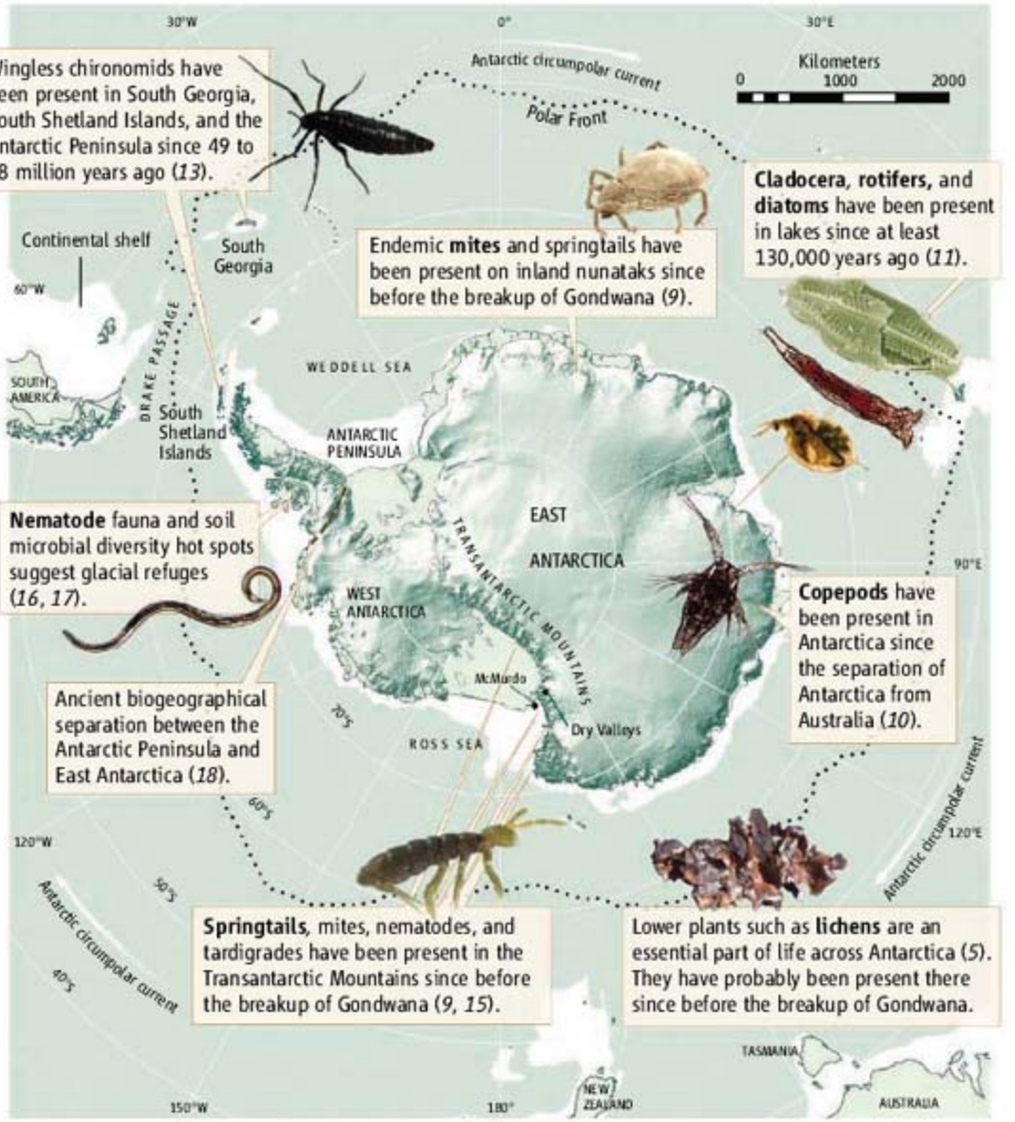
The latter view has been reinforced by the discovery of fossils that were referred to as the last surviving relicts from preglacial Antarctica (*3*, *4*). The fossils describe a community assemblage, including tundra vegetation and terrestrial and freshwater faunas, that survived the formation of the ice sheets initiated more than 30 million years ago but became extinct between 12 and 1.8 million years ago. The implication is that the terrestrial biota we see today consist of species that have become established since the Last Glacial Maximum.

A different picture emerges from early biological studies and some recent geological work. Baseline entomological research carried out in Antarctica as early as the 1960s (*5*–*7*) documented much of the arthropod biodiversity, particularly from the Transantarctic Mountains and the Antarctic Peninsula (see the figure). These authors recognized that at least a proportion of these biota could not easily be explained as recent colonists. Furthermore, in some isolated parts of continental Antarctica, reconstructions of previous glacial extent (*2*) do support the existence of



Ancient origins. Many organisms have persisted in Antarctica since well before the Last Glacial Maximum.

ice-free biological refuges at least from 1.8 million to 10,000 years ago. Evidence preserved from volcanic eruptions below the ice now also allows for the possibility of low-altitude ice-free land at glacial maxima (*1*, *8*).

More recent biological studies also point to much of the terrestrial biota having a long, continuous but isolated, history on the continent. Biogeographical analyses of freshwater copepods and nunatak-inhabiting mites (*9*, *10*) have identified distribution patterns consistent with evolutionary persistence in Antarctica over time scales between the Last Glacial Maximum and the final stages of Gondwana breakup (~40 to 60 million years ago), when Antarctica became isolated from South America and Australia. Other studies describe communities as having developed over the past 1.8 million years (*5*, *7*, *11*, *12*).

Recent molecular studies provide evidence for the persistence of several species on multimillion-year time scales (even back to pre–Gondwana breakup). For example, closely related chironomid midges endemic to tectonically distinct parts of the Antarctic Peninsula and Scotia Arc persisted for about 50 million years (*13*), revealing a biological signal of the separation of Antarctica and South America (*14*). Likewise, ancient divergences between endemic springtails from East Antarctica suggest radiation from a fauna dating from at least 21 to 11 million years ago (*15*). Even nematodes, which are capable of long-distance dispersal and gene flow (*16*), are endemic species isolated within the confines of continental Antarctica (*17*). Collectively, these studies provide evidence that terrestrial biota persisted in both the Antarctic Peninsula and East Antarctica, suggesting separate and ancient origins for these biota (*18*).

Thus, reexamination of the existing literature provides robust support for ancient origins of Antarctic terrestrial biota across most parts of the continent and involving most extant higher taxa (see the figure). Understanding the evolution and biogeographical history of the Antarctic terrestrial biota—especially in coastal areas—requires a more detailed multidisciplinary study of the persistence of terrestrial habitats than the current generation of ice sheet models permits. Terrestrial biological evidence could help researchers to improve glaciological reconstruction modeling and to gain further understanding of the evolution of the Antarctic continent.

Mountains in the Antarctic Peninsula. Terrestrial and freshwater biota have survived through glacial cycles in parts of the Peninsula.

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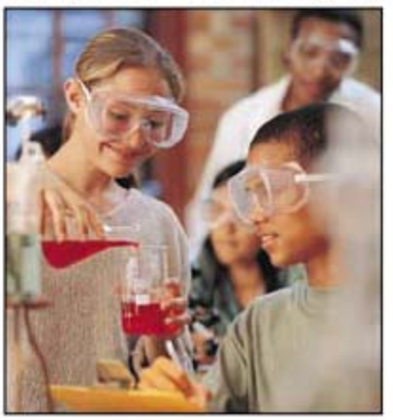
EDUCATION

AAAS Calls for National Standards As No Child Left Behind Testing Starts

American public school students will add one more important exam to their academic calendars this year: the first science assessments required by the national No Child Left Behind (NCLB) law. Under the 2001 statute, school districts must test students in science at least once in each of three grade spans: 3 to 5, 6 to 9, and 10 to 12. But in the absence of national standards for these tests, the exams vary from state to state, and AAAS experts say some of the tests may not make the grade.



In a 15 August op-ed in the *Washington Times*, AAAS CEO Alan I. Leshner urged U.S. lawmakers to "scrap the crazy-quilt pattern of wildly differing tests and proficiency thresholds that currently vary from state to state" and adopt voluntary national standards in science and math education as NCLB testing approaches.

Earlier this year, AAAS thanked Representative Vernon Ehlers (R–MI) and Senator Chris Dodd (D–CN) for their sponsorship of the SPEAK Act, which favored voluntary national standards. Variations in state learning standards and tests "make it difficult for parents and teachers to meaningfully gauge how well their children are learning mathematics and science in comparison to their peers internationally or here at home," the SPEAK authors concluded.

National standards for science education would not be hard to come by, Leshner noted in the op-ed, as AAAS and other organizations such as the National Research Council, the National Council of Teachers of Mathematics, and the National Assessment of Educational Progress have worked on these guidelines for several decades.

"There are two challenges that states must meet," explained George DeBoer, deputy director of Project 2061, AAAS's science literacy initiative. "The first is to develop high-quality standards. The second is to develop assessments that are aligned to those standards." Project 2061's surveys show that questions on many state assessment tests are unrelated to the key science concepts and skills outlined in AAAS's *Benchmarks for Science Literacy* and the National Research Council's *National Science Education Standards*.

Supported by a 5-year U.S. National Science Foundation grant, Project 2061 and its collaborators are building a database of appropriate multiple-choice items and open-ended questions for middle school and early high school students that states could use as a guide in developing their NCLB tests. The group has used science curricula and education experts, interviews, and pilot testing of hundreds of students to develop questions that target specific, standards-based concepts without confusing students with unclear language or too much jargon.

"When we talk about the work we're doing, people get excited about the high quality of the test questions and the precision of the alignment of those questions to content standards," DeBoer said.

The start of NCLB science testing highlights the need for higher-quality state tests, Project 2061 Director Jo Ellen Roseman wrote in a recent newsletter on the project, since the assessments "will only provide meaningful information if they are truly aligned to important science ideas, such as those in national benchmarks and standards."

While experts worry over readying the exams, the new testing requirements may not be a priority yet for school boards. Connie Bertka, program director of AAAS's Dialogue on Science, Ethics and Religion, oversees a 3-year project by AAAS and the National School Boards Association working with local school boards to make science education a community priority. She offered this anecdote: At a June meeting with local school board members in Kansas City, she "did not hear a lot of questions about how to get kids ready for NCLB testing."

Instead, the members that Bertka met were focused on ways to attract more resources to their district, particularly more high-quality science teachers. "I think it's still too far away for them—the tests have to be taken, the results have to be in," she said. "They have so many other things on their plate that they can't afford to get worried about this yet."

The NCLB law requires annual state testing in reading and mathematics for grades 3 through 8 in federally funded schools. Schools that do not score up to statewide standards in these subjects can face a range of corrective actions, from curricula changes to school closure. The first science tests must be completed by the end of the 2007-2008 school year.

Congress is keeping national science standards and the new tests in mind as it considers reauthorization of the NCLB law this fall. One version of the reauthorization bill, sponsored by Senators Joe Lieberman (I–CN), Mary Landrieu (D–LA), and Norm Coleman (R–MN), calls for voluntary science and mathematics standards based on recommendations by the U.S. Department of Education's National Assessment of Educational Progress. A proposed amendment sponsored by Ehlers and Representative Rush Holt (D–NJ) would add science exam scores to the reading and mathematics scores used to calculate a school's overall yearly progress report.

—*Becky Ham*

AAAS

New Mission Statement Focuses on Global Service, Leadership

The AAAS Board of Directors has revised the Association's mission statement emphasizing leadership on national and international scientific issues, the important role of engineers in its membership, and its commitment to science serving society.

The amended statement, adopted 20 August, reflects a 5-year expansion in AAAS's strategic role that includes broadening its international leadership activities and its role as scientific advisor in a variety of societal issues, from education to national security to health care. The revised statement also addresses changes in the scientific workforce, the proliferation of technology, and challenges to the integrity of science.

AAAS's mission statement has evolved substantially since its first constitution in 1856, in keeping with the growth of the U.S. scientific community and the rise of science and technology in public life. Some of the original "rules and objects" of the Association, such as fostering

communication between researchers and supporting the scientific enterprise, remain a priority.

The new statement

Mission: To advance science, engineering, and innovation throughout the world for the benefit of all people.

Goals:

- Enhance communication among scientists, engineers, and the public;
- Promote and defend the integrity of science and its use;
- Strengthen support for the science and technology enterprise;
- Provide a voice for science on societal issues;
- Promote the responsible use of science in public policy;
- Strengthen and diversify the science and technology workforce;
- Foster education in science and technology for everyone;
- Increase public engagement with science and technology; and
- Advance international cooperation in science.

—Becky Ham

SCIENCE POLICY

S&T Fellows Push for Impact on Sustainability

On the first morning of orientation for the new class of AAAS Science & Technology (S&T) Policy Fellows earlier this month, climate and energy scientist Holmes Hummel invited all Fellows interested in climate change, energy, and environmental issues to a lunchtime get-acquainted meeting.

Holmes Hummel, Lekelia "Kiki" Jenkins, Joshuah Stolaroff

Of 116 new Fellows, 35 showed up—a clear signal that sustainability issues are a galvanizing concern for many of the scientists and engineers who will serve in 1-year positions in Congress and a broad array of federal agencies.

"What I witnessed was a type of resolve," said Hummel, a Congressional Fellow. "For the last 10 years we've heard from every corner of social leadership that climate change and national security issues, related, will be major problems for our generation. Now we're seeing more early-stage career scientists answering the call."

For 34 years, the AAAS S&T Policy Fellowships have matched scientists and engineers in a range of fields—from agriculture and atomic physics to science education and defense technology—with executive branch agencies and congressional offices in Washington, D.C., that are seeking scientific expertise. Hundreds of Fellows have continued on to build high-impact careers in government, while others have moved into leadership positions in academia, nonprofit organizations, and the private sector.

In all, there are 162 Fellows this year, including 46 who are remaining with the Fellowship for a second year. Their interest in climate and sustainability issues continues a trend: 2 years ago, a group of Fellows met monthly to address sustainability and water issues; last year, a group met regularly to share resources and collaborate on sustainability problems, including climate change.

"Although the Fellows represent diverse scientific and engineering disciplines, they typically come to Washington to apply their expertise to the societal challenges of the times," said Cynthia Robinson, director of the Fellowships. "We're pleased to see this trend continue as climate change and related sustainability and security issues gain more recognition nationally and internationally."

In interviews, several 2007-08 Fellows said they wanted to explore multidisciplinary life beyond the lab. They're drawn to work that crosses disciplines. They tend to have a streak of idealism, and some expressed frustration that U.S. policy has blocked progress on critical sustainability challenges.

Before she became a Fellow in 2006, Adrienne Huston made four trips to the Arctic and spent two postdoctoral years at the University of Belgium in Liège for research focused on how the enzymes emitted by some Arctic bacteria can affect global carbon dioxide levels. Much of her research involved international collaboration, and she has become an advocate of science diplomacy. This year, she renewed her fellowship for a second year in the Office of International Science & Engineering at the National Science Foundation.

"I want to understand how science is done in a society," Huston explained. "Where do we want to be in 20 years, and how do we get there?"

Lekelia "Kiki" Jenkins says that sustainability issues will comprise an important part of her Fellowship work with the Marine Fisheries Service of the National Oceanic and Atmospheric Administration. Her scholarly work had been in marine conservation and related technologies, but she suspected that the pursuit of tenure might be limiting.

"I don't want to have to compromise and spend 5 or 7 years doing work that someone else tells me is important before I can get down to doing the things that are really going to affect the quality of life for people and animals in this world," Jenkins said.

The conventional wisdom is that federal science policy is in the doldrums, but several of the Fellows described this as a time of opportunity. Critical measures on climate change, energy, and environmental policy will be debated in Congress this fall, and the White House recently has signaled readiness to act more aggressively on such issues.

Joshuah Stolaroff has done much of his research in climate policy and CO_2 sequestration technology, and he'll work for the next year in the Environmental Protection Agency Office of Solid Waste and Emergency Management. He expects that Fellows will provide valuable expertise while the nation's political climate is changing.

"Energy and climate issues have been important for at least 5 or 10 years, but this year we're seeing that the public really knows that they're important," Stolaroff said. "There's a lot of momentum building. It's very encouraging as a scientist to know that there's public support for the things you've been working on."

COMMUNICATION

Science: An Advance for Green Publishing

Subscribers are reading a greener copy of *Science* these days, thanks to a recent switch to recycled paper for its pages. Introduced in April, the new paper stock is made from 30% post-consumer materials. The stock is also elemental chlorine-free, processed with chlorine dioxide instead of pure chlorine gas, which reduces the toxic by-products of paper pulp bleaching

The journal is now a bit slimmer, but "the most significant change that readers might notice is that the paper doesn't have a coating," said James Landry, *Science's* production director. The matte paper reduces reading glare and "is easier on the eyes," he explained.

Science Executive Editor Monica M. Bradford began a search for greener alternatives after attending a session on recycled paper at the 2006 meeting of the Council of Science Editors. "Our content makes it clear that we are pro-environment. I thought that it was important that *Science* practice what it preaches to the extent possible," Bradford explained.

In keeping with *Science's* international reach, the new paper has a multinational pedigree of its own. The stock is manufactured by Finnish paper company UPM at their Augsburg, Germany, mill before being shipped to the journal's long-time U.S. printers, Brown Printing Company in Waseca, Minnesota.

Brown was awarded Forest Stewardship Council (FSC) chain-of-custody certification for all three of its print locations in the United States in 2007. FSC certification ensures that the paper products used by Brown come from materials harvested in a forest managed according to a strict set of environmental standards.

—Becky Ham

Fluorine in Pharmaceuticals: Looking Beyond Intuition

Klaus Müller,[1]* Christoph Faeh,[2] François Diederich[2]*

Fluorine substituents have become a widespread and important drug component, their introduction facilitated by the development of safe and selective fluorinating agents. Organofluorine affects nearly all physical and adsorption, distribution, metabolism, and excretion properties of a lead compound. Its inductive effects are relatively well understood, enhancing bioavailability, for example, by reducing the basicity of neighboring amines. In contrast, exploration of the specific influence of carbon-fluorine single bonds on docking interactions, whether through direct contact with the protein or through stereoelectronic effects on molecular conformation of the drug, has only recently begun. Here, we review experimental progress in this vein and add complementary analysis based on comprehensive searches in the Cambridge Structural Database and the Protein Data Bank.

Fluorinated compounds are the least abundant natural organohalides (*1*). Most terrestrial F is bound in insoluble form, hindering uptake by bioorganisms. Until 1957, no F-containing drug had been developed. Since then, over 150 fluorinated drugs have come to market and now make up ~20% of all pharmaceuticals (*2*–*5*), with even higher figures for agrochemicals (up to 30%) (*4*). Top-selling fluorinated pharmaceuticals include the antidepressant fluoxetine (Prozac) (*6*), the cholesterol-lowering drug atorvastatin (Lipitor) (*7*), and the antibacterial ciprofloxacin (Ciprobay) (*8*) (Fig. 1).

Chemists have known about F's inductive effects for decades from small molecule studies (such as Hammett linear free-energy relationships). Also, F's capacity to enhance metabolic stability (mainly by lowering the susceptibility of nearby moieties to cytochrome P450 enzymatic oxidation) has become increasingly clear recently (*9*). In contrast, an understanding of how F affects binding affinity and selectivity at the molecular level is just starting to develop. Here, we highlight recent findings of F···protein interactions and complement the discussion with the analysis of structures in the Cambridge Structural Database (CSD) and the Protein Data Bank (PDB).

Structural information is essential for rationalizing F contributions to protein binding affinity. Taking the three pharmaceuticals mentioned above as examples, the CF_3 group in fluoxetine (table S1, entry 1) and the F substituents in atorvastatin and ciprofloxacin enhance potency, but this gain can be explained with confidence only for atorvastatin, which has been structurally characterized bound to its target. Atorvastatin (median inhibitory concentration = 8 nM) inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an essential enzyme in the biosynthesis of cholesterol. In an early stage of development, a series of inhibitors featuring a pyrrole core similar to the one in atorvastatin was screened. The 4-fluorophenyl derivative was found to be superior to ligands with hydroxy (by a factor of 2), hydrogen (factor of 5), or methoxy (factor of 10) groups in this position; only the chlorinated ligand was of similar potency (*10*). The x-ray crystal structure of atorvastatin bound to HMG-CoA reductase (table S1, entry 2) revealed that the aromatic C–F of the ligand approaches the guanidinium side chain of Arg590, [distance d(F···C(N3) = 2.9 Å)], hinting at a favorable polar interaction (*11*) discussed in detail below. Although published structure-activity relationships for quinolone antibiotics (*12*) such as ciprofloxacin might again hint at a favorable polar interaction of the essential F substituent at position 6, the absence of structural information limits confirmation of any such hypothesis (for the structure of ciprofloxacin bound to the AcrB multidrug efflux pump, see table S1, entry 3).

Synthetic Advances

Long after Moisson's preparation of elemental F_2 in 1886, its extreme reactivity still limited widespread laboratory fluorinations. This situation changed around 1970 with the introduction of safe and selective fluorinating agents that were compatible with ordinary laboratory equipment and therefore amenable to elaboration of lead compounds (*13*–*15*).

Today, an increasing number of such agents are directly available to researchers from commercial suppliers. Examples of nucleophilic reagents used to form C–F bonds (Fig. 2A) include diethylaminosulfur trifluoride (DAST) (*16*), 2,2-difluoro-1,3-dimethylimidazolidine (DFI) (*17*), and bis(2-methoxyethyl) aminosulfur trifluoride (Deoxofluor) (*18*); these reagents transform alcohols into monofluorides and carbonyls into gem-difluorides. A wide range of electrophilic reagents bearing a R_2N–F or R_3N^+–F unit has also been developed and commercialized, elaborated from the first such agent, pyridinium poly(hydrogen fluoride) (Olah's

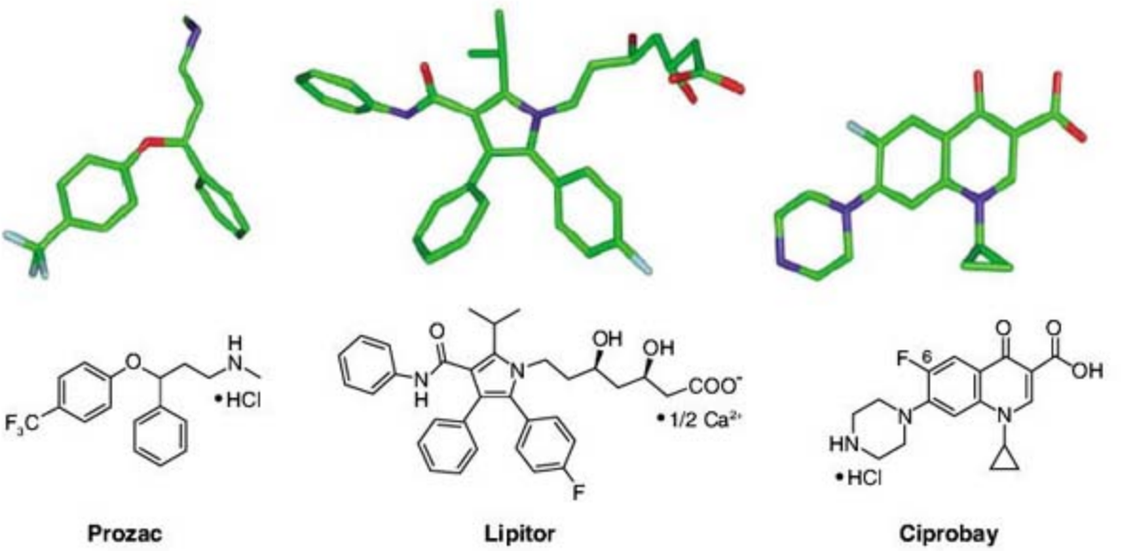


Fig. 1. Major fluorinated drugs: the antidepressant Prozac (table S1, entry 1), cholesterol-lowering drug Lipitor (table S1, entry 2), and quinolone antibiotic Ciprobay (table S1, entry 3). The molecular-model conformations are from crystal structures. Ligand Cs, green; O atoms, red; N atoms, dark blue; and F atoms, light blue. Unless otherwise stated, this color code also applies to the images in Figs. 3 and 5 and the supporting online material (SOM). Images generated with MacPyMol (*68*).

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reagent) (*13*). Examples (Fig. 2B) include 1-chloromethyl-4-fluorodiazoniabicyclo [2.2.2]octane bis(tetrafluoroborate) (Selectfluor) (*13*) and *N*-fluorobenzene-sulfonimide (NFSI) (*13*). Trifluoromethyl groups are conveniently introduced with trimethyl(trifluoromethyl)silane (Ruppert-Prakash reagent) (*13*) or the more recently developed trifluoroacetamides (Fig. 2C) (*19*). Protocols for asymmetric fluorinations are also expanding (*20*). Nevertheless, most of these reagents are too expensive for plant-scale production, where traditional methods such as the use of elemental F prevail.

Physical and Pharmacokinetic Properties

Fluorine is the most electronegative element. The C–F bond is one of the strongest known (table S2), and adjacent C–C single bonds are also strengthened, whereas allylic C=C double bonds are weakened by F substitution (*21*). The very low polarizability of organofluorine substituents also impacts intermolecular interactions (*22*). Further, the nuclear magnetic resonance (NMR) activity of F's sole natural isotope, ^{19}F, is convenient for characterization (*23*).

Fluorine often replaces H in organic molecules but the size and stereoelectronic influences of the two atoms are quite different (for bond lengths and van der Waals radii and volumes, see table S2). The bond length of C–F (1.41 Å) is actually more similar to C–O (1.43 Å) than to C–H (1.09 Å), although packing-radius comparisons are a subject of ongoing research (*24*). The van der Waals volume of the trifluoromethyl (CF_3) group (as in fluoxetine) is similar to that of the ethyl group (CH_3CH_2) but the shapes of the two groups are very different. Despite suggestions that CF_3 and isopropyl [$(CH_3)_2CH$] are interchangeable (*21*), isopropyl has a larger volume and is axially anisotropic (*25*).

Bioisosterism is an important concept in lead optimization. It refers to the capacity of atoms or functional groups with similar sizes or shapes to be interchanged without substantially altering biological behavior such as binding affinity (*26*). Thus, the fluorovinyl group (C=CHF) has been used as a replacement for the peptide bond (*27*). Fluorine takes the position of the carbonyl O, and the planarity of the vinyl unit makes it quite a good match in size and geometry, as shown in the inhibition of dipeptidyl peptidase IV. The C–F bond length and the total extension of a C–F unit are similar to the values for the C=O group (table S2). The C–CF_3 fragment has also been introduced as a substitute for the C=O group, providing a substantial gain in potency of cathepsin K inhibitors (*28*). The C–F and C–O dipoles can undergo similar multipolar interactions with neighboring dipoles.

Bioisosterism of C–F, C–OH (*29*), and C–OMe (where Me is methyl) was also observed for a series of tricyclic inhibitors of thrombin, a Ser protease from the blood-coagulation cascade (*30*). Similar potency was found for inhibitors in which any of the three groups were bound at specific positions on the central scaffold so as to point into the region of the catalytic triad and the oxyanion hole of the enzyme. C–F, C–OH, and C–OMe thus appear to be bioisosteric (in terms of binding efficacy) if the negative poles (O, F) interact with the positive pole of another dipole or a positively charged center, provided that the Me group of C–OMe can be accommodated without strain and that the OH group finds a H-bond acceptor. A striking example of this analogy between C–OH and C–F has also been noted (*11*) in a crystal structure of a HIV protease complex with a bound peptidic inhibitor containing a central α-difluoroketone hydrate unit (table S1, entry 4).

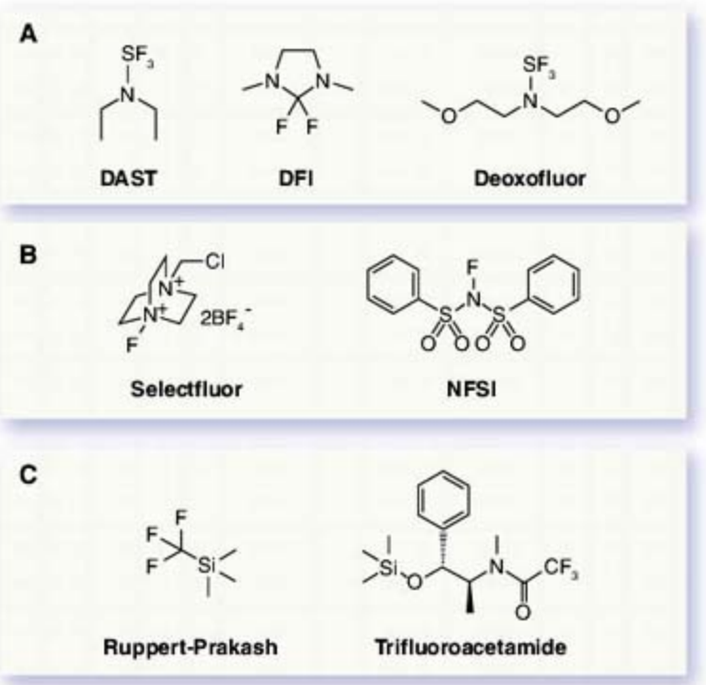


Fig. 2. Examples of safe and selective fluorination agents. **(A)** Nucleophilic agents, **(B)** electrophilic agents, and **(C)** reagents to introduce CF_3 groups.

Conformational and Stereoelectronic Influences

Knowledge about the energetically most favorable conformation of a ligand is essential for optimizing the binding efficacy, which increases with the ligand's degree of preorganization: The more closely the geometry of the bound ligand resembles the lowest-energy conformation of the free ligand, the stronger the gain in binding free energy. Ligand preorganization usually translates into enforcing the most favorable conformation through rigidification. When binding a preorganized ligand, no enthalpy loss occurs to reach the favorable binding geometry, and there is no need to freeze out the desirable binding conformation in an entropically unfavorable way. Conformations of free ligands are usually determined experimentally in solution by ^1H NMR measurements, and this information is frequently complemented by gas-phase theoretical calculations and conformational searches in the CSD (*31*, *32*). Information on the conformation of bound ligands is usually extracted from protein-ligand cocrystal structures.

Substitution of H by F can profoundly change the conformational preferences of a small molecule because of size and stereoelectronic effects. A comparison between methoxyphenyl and trifluoromethoxyphenyl groups illustrates the influence of F on conformation. Methoxy groups lie in the plane of the phenyl ring because the p orbital of the sp^2-hybridized O is in π conjugation with the aromatic π system. This conformation is preferred by ~3.0 kcal/mol (*33*, *34*). In contrast, trifluoromethoxy groups tend to turn out of plane because of their larger size and, presumably more substantially, stereoelectronic effects. Orienting C–F bonds antiperiplanar to the lone pairs of the now sp^3-hybridized O results in an anomeric n_O–σ^*_{CF} conjugation with concomitant lengthening of the C–F bonds (*35*). This effect reduces the conjugation between O and the aromatic π system and eliminates the energetic preference of a planar, in-plane conformation.

Computational studies and searches in the CSD (fig. S1) (*31*, *32*) and the PDB (*36*) were carried out to investigate the conformational preferences of aromatic OCH_3, OCH_2F, $OCHF_2$, and OCF_3 groups. Only cases in which at least one ortho position of the aromatic ring was unsubstituted were considered, as two non-H ortho groups lead to orthogonal orientations of all alkoxy groups for steric reasons. Neither CSD nor PDB searches yielded any structures with aryl–OCH_2F motifs; computational studies revealed (*33*, *34*) two conformational energy minima with dihedral angles θ [C_{aryl}–C_{aryl}–O–$C(H_2F)$] of 24° (ΔE_{rel} = 0.0 kcal/mol) and 0° (ΔE_{rel} = 4.2 kcal/mol). Whereas the high-energy conformation is predicted to be planar without an anomeric effect, the low-energy twisted conformation has the C–F unit in an anomeric arrangement. Overall, the change from OCH_3 to OCH_2F reduces the in-plane conformational preference.

The CSD search provided seven aryl–$OCHF_2$ fragments, with torsional angles [C_{aryl}–C_{aryl}–O–$C(HF_2)$] between 1° and 90°. Thus, there seems

to be no orientational preference, as was also confirmed by calculations that afforded equal-energy minima at θ = 33° and 90°. The orthogonal conformation has both C–F bonds in an anomeric (endo) orientation similar to the trifluoromethoxy group, whereas the twisted conformation is predicted to have only one C–F bond in an anomeric position (with a slightly longer C–F bond length than the nonanomeric C–F bond). This prediction is particularly nicely borne out by a crystal structure (table S1, entry 5) in which the asymmetric unit contains two independent molecules, one with an approximate orthogonal conformation (θ = 86°) with two anomeric C–F bonds, the other with a twisted arrangement (θ = 58°) and only one anomeric C–F bond. This structure provides experimental evidence that the two conformations cannot be largely different in energy as they coexist within the same crystal. Seven structures in the PDB feature ligands with aryl–$OCHF_2$ fragments (table S1, entries 6 to 11). The measured dihedral angles vary from θ = 0° to 50°. Three of the seven x-ray crystal structures were complexes of phosphodiesterase 4 with roflumilast (DAXAS), a drug against respiratory diseases that was withdrawn from the market in 2005 (Fig. 3) (*37*).

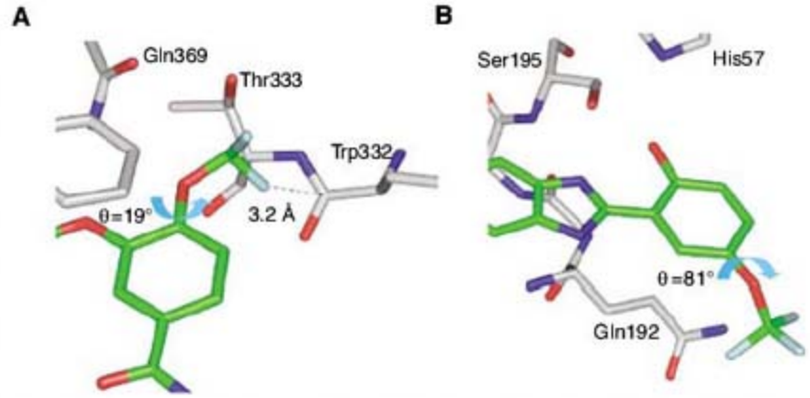


Fig. 3. **(A)** Aryl–$OCHF_2$ fragment (θ = 19°) of roflumilast bound to phosphordiesterase 4 (table S1, entry 7) shows a multipolar C–F···C=O contact with the backbone amide of Trp332. **(B)** Aryl–OCF_3 fragment (θ = 81°) of an inhibitor bound to the Ser protease trypsin (table S1, entry 13). Protein Cs are shown in gray (also applies to Fig. 5 and the SOM).

Thirteen structures with aryl–OCF_3 fragments were found in the CSD. The majority show a preference for a dihedral angle C_{aryl}–C_{aryl}–O–$C(F_3)$ of θ ≈ 90°. Thus the O–CF_3 bond seems to prefer an orthogonal orientation to the aromatic plane, although the calculations suggest that the energetic differences in the dihedral-angle range of 0° to 90° are small (~1 kcal/mol). The PDB contains eight structures with aryl–OCF_3 fragments (table S1, entries 12 to 19); six have a dihedral angle θ between 81° and 86°, so here too we see a preference for orthogonal alignment of the O–CF_3 bond (Fig. 3). The one structure in the CSD (table S1, entry 20) with an aryl–SCF_3 bond also shows a 90° dihedral angle.

The introduction of F into piperidine rings decreases the basicity of the N center (*38*), thereby improving oral bioavailability, as has been shown for ligands of the human 5-HT_{1D} receptor, a target in migraine therapy (*39*), and for antagonists of the h5-HT_{2A} receptor, a target in schizophrenia therapy (*40*). Fluorine in protonated 3-fluoro- and 3,5-difluoropiperidines strongly prefers the axial position in aqueous solution, whereas after deprotonation, the F substituent adopts an equatorial position (*41*, *42*). In the axial orientation, the polar C–F and N^+–H fragments undergo favorable antiparallel dipolar interactions. These intramolecular interactions are quite effective, and the axial preference of 3-fluoro- substituents is maintained in protonated 3-fluoro-*N*-alkylpiperidinium salts and even in quaternary 3-fluoro-*N*,*N*-dialkylpiperidinium salts, despite steric congestion.

Influence of logD and pK_a Effects

Biological absorption and distribution are largely controlled by the ionization state and balance of lipophilicity and hydrophilicity in a drug molecule. Enhanced lipophilicity can increase the measured binding free energy through more favorable partitioning between the polar aqueous solution and the less polar receptor site. A convenient measure of lipophilicity is the logarithmic coefficient (logD) for distribution (D) of a compound between octanol and water at pH 7.4. In general, H/F exchange leads to a more lipophilic molecule. The logD values of nearly 300 compounds have been measured, and they followed this trend (*43*). A single H/F exchange raises the logD value by approximately 0.25. A large increase in logD is usually seen when F is introduced nearby a basic N. Amine basicity is decreased because of the σ-inductive effect of F, and thus the ratio of neutral to protonated molecules increases.

However, there are exceptions wherein the introduction of F, in particular into aliphatic chains and rings, leads to a reduction in the logD value. LogD values sometimes decrease when F is introduced near O (*43*) or N atoms (*30*). Such a decrease was observed when the O···F distance of at least one low-energy conformer in a molecule was smaller than 3.1 Å, and this finding has been tentatively explained by solvation effects. On the other hand, replacement of a methoxy group by a trifluoromethoxy group attached to an aryl unit may result in a marked increase in lipophilicity as seen, for example, in the ΔlogP of 1.1 between trifluoromethoxy- and methoxybenzene [the logarithmic partition coefficient logP (octanol/water) and logD are identical for nonionizable solutes] (*44*). This finding can be explained by a primary H/F effect augmented by a depolarization and desolvation effect by the orthogonally oriented OCF_3 group, partially shielding one π face of the aromatic ring.

Also somewhat surprisingly, (3-fluoropropyl)-benzene and (3,3,3-trifluoropropyl)benzene are markedly less lipophilic than nonfluorinated propylbenzene, with ΔlogP = –0.7 and –0.4, respectively (fig. S2). This result can be explained by the introduction of polarity to a highly hydrophobic domain. In this example, the polarity effect is stronger for the monofluorinated analog than for the trifluorinated one.

Fluorine introduction also strongly reduces amine basicity, impacting membrane permeability (*45*), the potential liability for phospholipidosis (*46*), and interference with the *hERG* (*human ether a-go-go–related gene*) K^+ channel associated with cardiovascular toxicity (*47*–*49*). Useful predictive rules have been developed for tuning the pK_a values (where K_a is the acid dissociation constant) of basic amine centers through σ-transmission effects of F, O, N, and S functionalities (*38*, *50*). Thus, the pK_a value steadily decreases upon F introduction in the series $CH_3CH_2NH_2$ (10.7) → $FCH_2CH_2NH_2$ (9.0) → $F_2CHCH_2NH_2$ (7.3) → $F_3CCH_2NH_2$ (5.7) (*38*). A sufficient number of nearby F atoms can leave an amine unprotonated at physiological pH, resulting in higher bioavailability, as shown for inhibitors of the human 5-HT_{1D} receptor (*39*). In alicyclic systems, substantial conformational and stereoelectronic effects are only beginning to be identified and understood (*38*, *51*). For example, σ-transmission effects in five-membered rings (such as pyrrolidines) are only 70 to 80% as efficient as those in six-membered rings (such as piperidines), in which perfectly staggered conformations, similar to those of aliphatic chains, can be adopted (*38*).

Over the past 5 years, we have conducted a "fluorine scan" of tricyclic inhibitors of thrombin to map the fluorophilicity and/or fluorophobicity of the enzyme active site (*30*, *52*–*56*). Fluorine was systematically introduced at various positions of the inhibitor skeleton to explore specific interactions of the halogen with active-site amino acid residues of the enzyme. The binding mode of the tricyclic inhibitors at the thrombin active site was confirmed by several crystal structures of protein-ligand complexes and is schematically shown in Fig. 4 (*30*, *52*, *56*, *57*). Remarkably, the pK_a value of the tertiary-amine center in the inhibitors can be tuned from the usual value near 10 to less than 2, through σ-transmission effects of remote Fs. The pK_a value of the tertiary-amine center in tricyclic (±)**1** is 7.0, 3 units below the

approximate value for a simple trialkylamine (~10.2) and some 4 units below the pK_a of heliotridane, a methylated hexahydropyrrolizidine that is the closest comparison compound for the bicyclic fragment that incorporates the tertiary-amine center (*38*). This pK_a lowering results from the electron-withdrawing effects of the two imide carbonyl groups. The phenylamidinium moiety in (±)**2** reduces the pK_a value further by 2.5 units. Adding one F to the terminal five-membered ring [(+)**3** to (+)**6**] lowers the pK_a value to ~3.3. In each of these compounds, F is in both β and γ positions of the tertiary amine and thus draws electron density through two σ pathways. The pK_a reduction by OH [(+)**7**] and MeO [(+)**8**] groups is much less effective. The protonated difluorinated compounds (+)**9** and (±)**10** are even moderately strong acids ($pK_a < 2$).

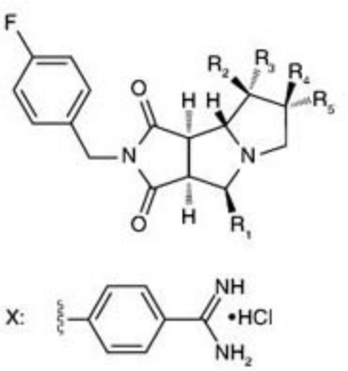
Carbonic anhydrase II is another enzyme for which organofluorine effects on physical properties and binding efficacies of aliphatic and benzenesulfonamide-based inhibitors have been extensively studied (*58*, *59*). The introduction of F near the sulfonamide (RSO_2NH_2) moiety increases the acidity of the N–H bond, facilitating deprotonation and stronger binding of the resulting anion to the Zn(II) ion at the active site of the enzyme. This point is nicely illustrated by comparing the inhibitory potency of weakly acidic methylsulfonamide ($CH_3SO_2NH_2$) [$pK_a \cong 10.5$, inhibition constant (K_i) = 10^{-4} M] to that of the much more acidic trifluoromethylated counterpart $CF_3SO_2NH_2$ ($pK_a = 5.8$, $K_i = 2 \times 10^{-9}$ M) (*60*).

Selective Protein-Ligand Interactions

Electronegativity considerations would suggest that C–F behaves similarly to C–O and C–N fragments and acts as a good H-bond acceptor. However, an extensive search of the CSD and the PDB revealed this not to be the case (*61*). The C–F unit is a poor H-bond acceptor: Organic F has a very low proton affinity and is weakly polarizable. Nevertheless, the large number of C–F···H–X (where X = O, N, S) as well as C–F···H–C_α (C_α carbon of α amino acids) contacts points to the fact that it is favorable for the C–F dipole to undergo multipolar interactions (*11*). C–F···H–N (backbone amide) interactions are abundant in the PDB (*36*). Out of 788 C–F containing structures, constraining the F···N separation below the van der Waals contact distance of $d_1 = 3.1$ Å and the angles $\alpha_1 \geq 150°$ and $90° \leq \alpha_2 \leq 150°$ gave 11 structures in which the C–F moiety of the ligand points toward the H–N bond (Fig. 5A). In the case of two thrombin inhibitors that differ by only one H/F substitution (*43*), the F-containing inhibitor is more potent by a factor of 5 and shows a dramatic conformational change in its bound state when compared to the nonfluorinated ligand (Fig. 5D and fig. S3). The crystal structures (table S1, entries 21 and 22) reveal for the fluorinated analog a dipolar C–F···H–N interaction with a distance of 3.5 Å, which could be responsible for the observed change in conformation. This distance is well beyond H-bonded contact distances, but the conformational change and the resulting gain in potency provide particularly strong evidence for energetically favorable dipolar interactions.

Orthogonal multipolar C–F···C=O interactions were nicely revealed during the fluorine scan of tricyclic thrombin inhibitors (*52*). Introduction of F in the para position of the benzyl ring occupying the D pocket of thrombin (Fig. 4) enhanced the binding affinity by a factor of 6 ($\Delta\Delta G = -1.1$ kcal mol^{-1}, where $\Delta\Delta G$ is the difference in binding free enthalpy between para-F-substituted and -unsubstituted ligands) (*52*). X-ray crystallography revealed (table S1, entry 23) that the C–F residue interacts not only at short distance with H–C_α [d(F···C 3.1 Å)] but also in an orthogonal fashion, with the backbone C=O group of Asn98 (Fig. 5C). Such orthogonal multipolar interactions were subsequently shown to be abundant in both small molecule x-ray crystal structures and in protein-ligand complexes (*11*, *54*), although they had not been recognized as such [for an early example, see fig. S4 (*62*)]. Investigations of a model system in chemical double-mutant cycles subsequently confirmed the attractive nature of the orthogonal C–F···C=O interaction, with a contribution in binding free enthalpy in apolar environments of $\Delta\Delta G = -0.2$ to -0.3 kcal mol^{-1}, about a third of the gain from a neutral H bond (*63*). Such contacts are observed for both aliphatic and

A



Compound	R^1	R^2	R^3	R^4	R^5	pK_a
(±)-**1**	H	H	H	H	H	7.0
(±)-**2**	X	H	H	H	H	4.5
(+)-**3**	X	F	H	H	H	3.4
(+)-**4**	X	H	F	H	H	3.3
(+)-**5**	X	H	H	F	H	3.3
(+)-**6**	X	H	H	H	F	3.3
(+)-**7**	X	OH	H	H	H	4.1
(+)-**8**	X	OMe	H	H	H	3.7
(+)-**9**	X	F	F	H	H	<2
(±)-**10**	X	H	H	F	F	<2

B

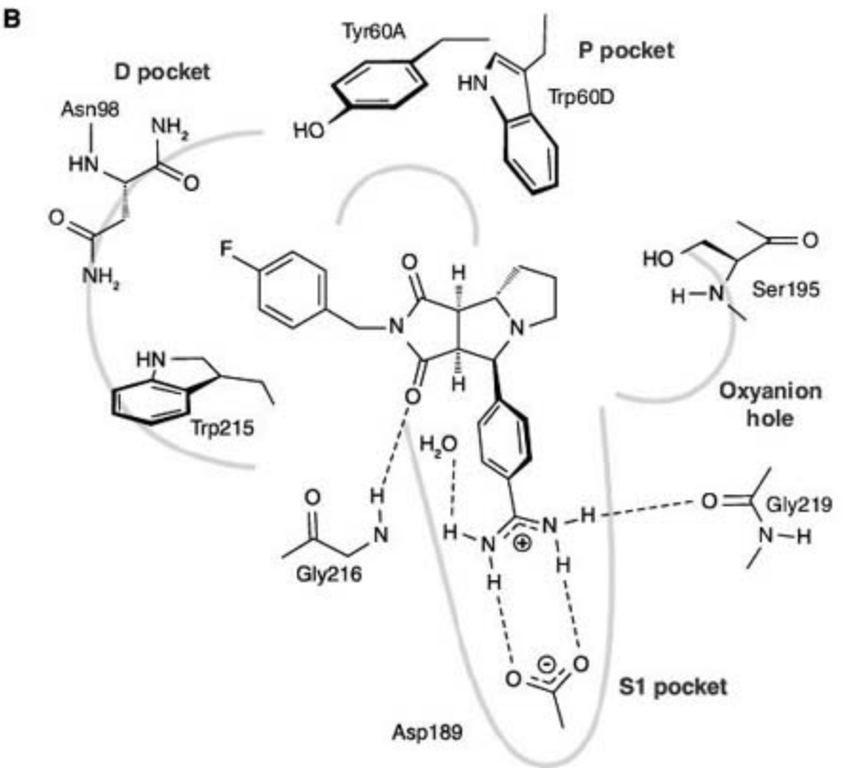


Fig. 4. (**A**) pK_a values for the tertiary-amine center in tricyclic inhibitors of the Ser protease thrombin. (**B**) Binding mode of the inhibitors as confirmed by x-ray crystal structures of protein-ligand complexes.

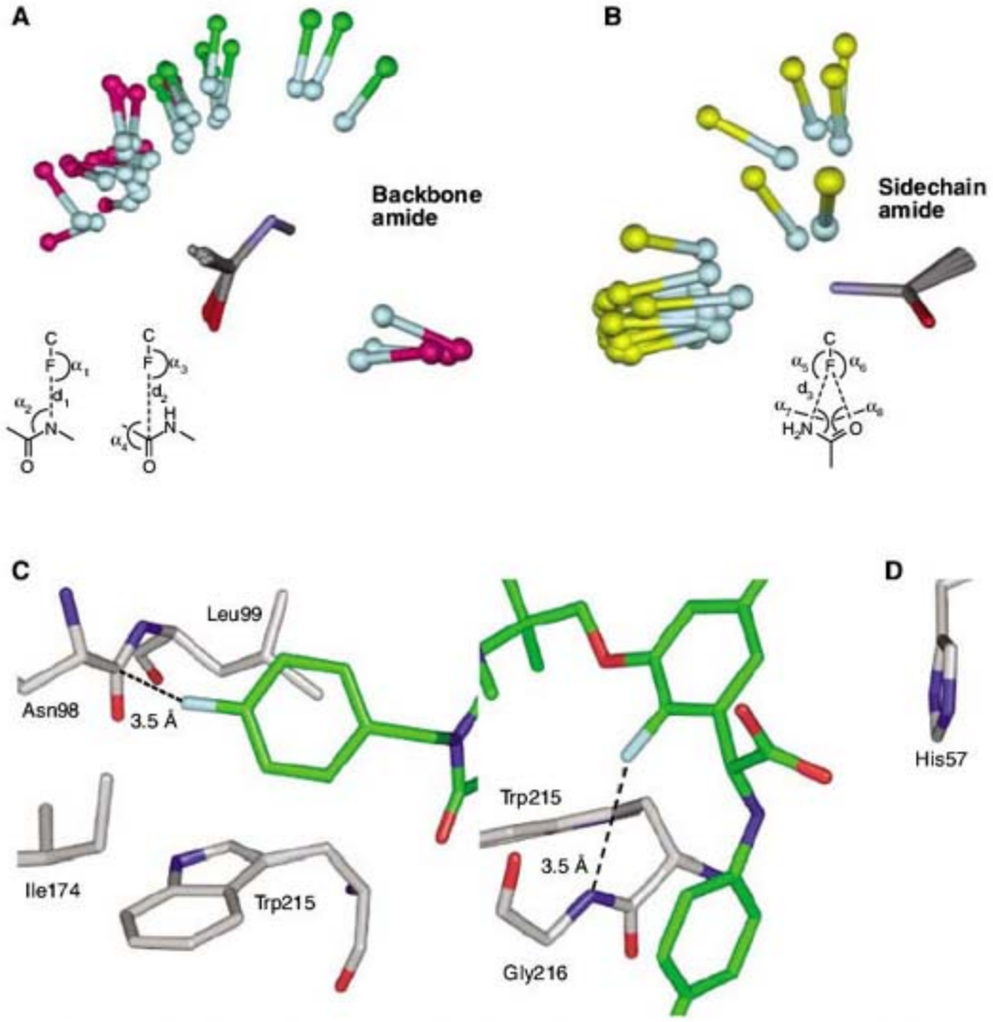


Fig. 5. **(A)** Fluorine interacts favorably with peptidic N–H (ligand Cs in green) and C=O (ligand Cs in purple) moieties. **(B)** Fluorine undergoes dipolar interactions with side-chain amides of Gln and Asp (ligand Cs in yellow). **(C)** The C–F residue of a tricyclic inhibitor undergoes a multipolar interaction with the backbone C=O of Asn98 in the D pocket of thrombin (table S1, entry 23). **(D)** A dipolar N–H···F–C interaction induces the shown conformation of a thrombin inhibitor within the enzyme (fig. S3 and table S1, entry 22).

aromatic C–F and are also seen for CF_3 groups. In the structure of an inhibitor of the trifluoroacetyl peptide class bound to porcine pancreatic elastase (table S1, entry 24), all three F atoms of the CF_3CO group interact in an orthogonal fashion with three backbone C=O groups of the protein. At short contact distance, orthogonal C–F···C=O interactions are much more frequent than the energetically more favorable antiparallel dipolar alignments (*11*), which can be explained by reduced steric hindrance.

An earlier search for orthogonal C–F···C=O interactions in the PDB (*11*, *54*) was repeated with an upper cutoff limit for the F···C distance of d_2 = 3.3 Å (Fig. 5A) and angles set to values of $\alpha_3 \geq 140°$ (C–F···$C_{C=O}$) and $70° \leq \alpha_4 \leq 110°$ (F···$C_{C=O}$=O). This search yielded 20 hits shown in Fig. 5A. Most of these hits also feature additional favorable C–F···H–C_α interactions below the van der Waals distance. An overlay of both C–F···H–N and C–F···C=O interactions illustrates how F organizes around backbone amides, which clearly provide a fluorophilic environment.

The new search also revealed a specific geometric preference for the interaction between C–F and side-chain amide residues of Gln and Asn. In 17 out of 23 hits, C–F points frontally onto the H_2N–C=O moiety, with the F···N distance as the shortest ($d_3 \leq 3.1$ Å). The O···F–C and N···F–C angles amount to $120° \leq \alpha_{5/6}$, whereas the $C_{C=O}$–N···F and $C_{C=O}$–O···F angles have values of $60° \leq \alpha_{7/8} \leq 150°$ (Fig. 5B). An example for this preferred interaction is found in the complex of endoglucanase Cel5A bound to a fluorinated inhibitor (table S1, entry 25); here, the F···N distance is 2.9 Å.

Beyond highlighting the favorable character of orthogonal C–F···C=O interactions, the fluorine scan of the thrombin inhibitors leads to some general conclusions about fluorophobic environments. C–F bonds pointing into highly polar environments such as the oxyanion hole of thrombin were found to reduce binding affinity. Also, C–F bonds avoid pointing directly at the O atom of C=O groups. Thus, the behavior of F contrasts with that of the larger, more polarizable halogens Br and in particular I, for which such linear C–X···O=C alignment is observed ("halogen bonding") (*11*). Tricyclic thrombin inhibitors directing fluoroalkyl and alkyl residues of appropriate and similar size into the narrow P pocket of thrombin, which is lined by the side chains of Trp60D, Tyr60A, and His57 (Fig. 4), gave similar binding affinities. However, overlays of crystal structures suggest that a CHF_2 group in the P pocket points away from the electron-rich π surface of the indole ring of Trp60D lining the pocket (*55*). A preference for positively polarized environments is consistent with F's high electronegativity.

This conclusion also finds support in a PDB search for C–F interactions with the guanidinium group of Arg, inspired by observations for the complex of atorvastatin bound to HMG-CoA reductase (table S1, entry 2). In many protein-ligand complexes, C–F bonds point toward the guanidinium moiety of Arg (fig. S5). However, no linear C–F···H–N interactions were observed, in agreement with the poor H-bond-accepting capacity of F. Instead, C–F bonds were found to orient either parallel to or more orthogonally to the guanidinium plane with its delocalized positive charge. A high total of 32 structures showed distances below 3.8 Å (the distance cutoff takes into account the longer range of interactions involving charges) between the F atom and the central C atom of the guanidinium residue, which clearly highlights the fluorophilic character of the Arg side chain.

Fluorine also affects the aromatic interactions of the phenyl ring to which it is attached. The positive polarization of neighboring ortho H atoms is increased, strengthening C–H···X (where X = O, N) and C–H···π interactions. Upon moving from benzene to hexafluorobenzene, the quadrupole moment changes with increasing fluorination from a large negative to a large positive value (*64*–*66*). In benzene, the negative poles are on the π surfaces and the positive poles on the C–H residues; in hexafluorobenzene, the charge distribution is exactly opposite. This distinction has strong implications for aromatic interactions. Benzene and hexafluorobenzene undergo efficient eclipsed face-to-face stacking interactions, which have been used as a construction principle in supramolecular chemistry (*67*). In medicinal chemistry, it was shown that face-to-face stacking interactions between the pentafluorophenyl ring of a 1,3,4-thiadiazole-2-thione-based inhibitor and Tyr155 of the metalloprotease stromelysin (table S1, entry 26) strongly contribute to the protein-ligand binding affinity. Nevertheless, a variety of electrostatic forces such as dipole-dipole, dipole-induced dipole, or dipole-quadrupole interactions may dominate quadrupole-moment interactions and induce other orientational preferences between aromatic and fluoroaromatic rings. Thus, a rare edge-to-face interaction between Phe131 and a perfluorophenyl ring was

seen in the crystal structure of an inhibitor bound to carbonic anhydrase II (table S1, entry 27).

Outlook

It is becoming clear that F can enhance binding efficacy and selectivity in pharmaceuticals. As small atoms of high electronegativity, F substituents on ligands prefer to orient toward electropositive regions of receptor sites. Distinct fluorophilic environments in proteins include the ubiquitous peptide bonds (particularly those in hydrophobic environments), which undergo multipolar C–F···H–N, C–F···C=O, and C–F···H–C_α interactions, as well as the side-chain amide residues of Asn and Glu and the positively charged guanidinium side chain of Arg. Correspondingly, F introduction into regions of high electron density can adversely affect the binding affinity. The introduction of fluoroalkyl substituents into tight lipophilic pockets lined by electron-rich aromatic rings neither increases nor decreases binding affinity substantially, as compared with similarly sized alkyl residues. However, taking into account advantageous effects on physicochemical properties, an overall benefit may well result from the decoration of ligands with fluoroalkyl residues to occupy apolar aromatic pockets. On the basis of these conclusions, we suggest systematic fluorine scans of ligands as a promising strategy in lead optimization, not only to enhance physicochemical and adsorption, distribution, metabolism, and excretion properties, but also to strengthen protein-ligand binding interactions.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/317/5846/1881/DC1
Figs. S1 to S5
Tables S1 and S2
References

10.1126/science.1131943

Correlated Evolution and Dietary Change in Fossil Stickleback

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Models, experiments, and field studies provide evidence of the ecological controls on evolution, but extrapolating results over longer time scales is a perennial problem in evolutionary biology. Trophic ecology and competition for food, for example, are thought to drive speciation through niche differentiation, character displacement, and phenotypic divergence (*1*). Yet direct evidence that feeding controls evolution over extended time scales, available only from the fossil record, is difficult to obtain because it is rarely possible to directly analyze dietary change in long-dead animals. Functional changes must be inferred from changes in morphology, and attempts to determine whether morphological changes were caused by shifts in feeding can become circular.

Here, we report an investigation of trophic resource use in a fossil sequence preserving an evolving lineage of threespine stickleback (*Gasterosteus*). We focus on stickleback for two reasons. First, perhaps the best-known work on speciation in fishes concerns stickleback in postglacial coastal lakes in Canada, where planktivores and benthic feeders coexist as two reproductively isolated and phenotypically distinct trophic forms. The differences between these forms result from competition for food (*1*, *2*). Second, fossil stickleback from the Miocene Truckee Formation (Nevada) provide a detailed, high-resolution record of evolutionary change within a lineage spanning tens of thousands of years (*3*).

We investigated the relationship between trophic resource use and evolutionary change through quantitative analysis of dental microwear (*4*). Laboratory feeding experiments and analyses of wild stickleback populations show that microwear exhibits a progressive shift from planktivores to benthic feeders (Fig. 1, A and B) (*5*). Discriminant analysis using feature length and density indicates that scores for the first discriminant function (DF) are a good predictor of trophic ecology. For wild fish populations (n = 4), mean scores were significantly correlated with diet (r = 0.95, P = 0.05) and gill raker number (r = –0.996, P = 0.004).

Analysis of fossil stickleback teeth revealed an overall range and pattern of feature densities and lengths similar to that of extant fish (Fig. 1C), suggesting that the fossil microwear records a similar benthic-planktonic feeding spectrum. This was supported by application of the DF derived from wild fish to the fossils: DF scores vary significantly between samples (F = 10.8, df of 7 and 87, P = 0.0001), and a Tukey-Kramer procedure revealed significant pairwise differences. This procedure also grouped some fossil samples with benthic-feeding wild populations (samples 19.6, 19.7, 19.6, and 6.9), others with planktivore populations (21.5), with some placed between (2.9 and 3.8).

These changes in inferred trophic ecology are significantly correlated with evolutionary changes in armor phenotype through time (*3*) (Fig. 1E). DF scores are correlated with dorsal [nonparametric Spearman rank correlation (r_s) = 0.23, P = 0.03, n = 89 fish] and pelvic armor (r_s = 0.21, P = 0.05), feature density with dorsal armor (r_s = 0.24, P = 0.02). Interestingly, the shift to a more benthic ecology within sample 19.8 (Fig. 1, D and E) precedes the increase in mean armor scores in 19.6 (a time lag of circa 100 years). This evidence of an ecological shift preceding phenotypic change suggests that this part of the sequence may record rapid evolution driven by shifts in trophic ecology and adaptation to benthic niches. If this hypothesis is correct, however, the low number of specimens displaying intermediate phenotypes is puzzling, and the scenario of replacement of one lineage by another (*3*) cannot be ruled out. The gradual shift to less benthic ecology over the next 17,000 years supports the interpretation that a return to low-armor phenotypes reflects directional natural selection (*3*).

Our analysis shows that dental microwear analysis can provide direct evidence for changes in trophic niche and resource exploitation in fossil fishes. That changes in feeding can be detected independently of morphological change highlights the potential of this approach to provide important insights into trophic ecology during adaptive radiations of fishes and other evolutionary events.

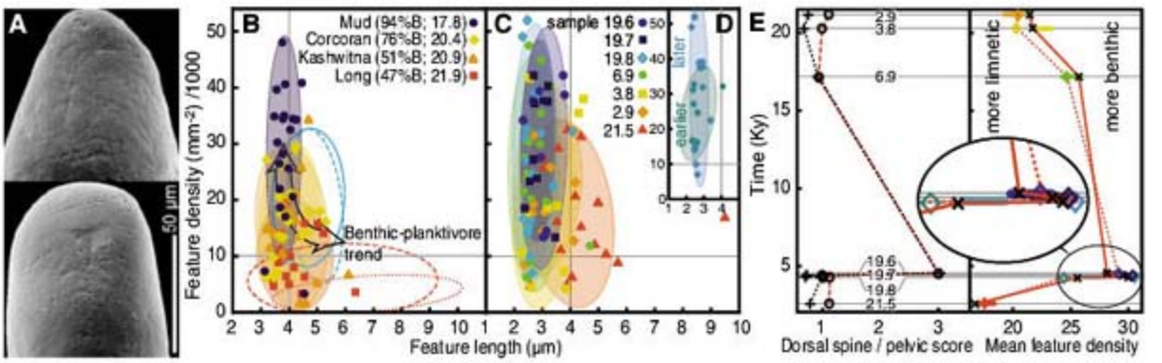

Fig. 1. Microwear in stickleback teeth and correlated evolutionary change. **(A)** Scanning electron micrographs showing tooth microwear in fossil (top) and extant benthic feeding (bottom) stickleback. For details, see fig. S1. **(B)** Microwear in wild-caught and lab-raised stickleback. Open ellipses indicate lab distributions (blue, benthic treatments; red, planktivore; solid, dashed, and dotted lines are course, medium, and no sand substrate, respectively). In wild fish, microwear tracks trophic ecology as indicated by % benthic stomach contents and mean gill raker count (Mud Lake, most benthic; Long Lake, least benthic). **(C)** Fossil stickleback microwear; inset **(D)** shows sample 19.8 divided into earlier (1746 to 1753 years) and later (1757 to 1771 years) subsamples with shift toward more benthic trophic ecology in later interval. Ky, thousand years. **(E)** Trophic niche and morphology in fossil stickleback through time [○ dorsal armor; + pelvic armor; ◇ mean feature density; × DF scores (minimum of 0.38 and maximum of 2.51)]. Colored horizontal bars show niche scores reflecting the position of the samples in the benthic-planktivore microwear spectrum (C). Time scale follows (*3*).

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The Dark Side of the Rings of Uranus

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The rings of Uranus are oriented edge-on to Earth in 2007 for the first time since their 1977 discovery. This event provides a rare opportunity to observe their dark (unlit) side, where dense rings darken to near invisibility, but faint rings become much brighter. We present a ground-based infrared image of the unlit side of the rings that shows that the system has changed dramatically since previous views. A broad cloud of faint material permeates the system but is not correlated with the well-known narrow rings or with the embedded dust belts imaged by the Voyager spacecraft. Although some differences can be explained by the unusual viewing angle, we conclude that the dust distribution within the system has changed substantially since the 1986 Voyager encounter and that it occurs on much larger scales than has been seen in other planetary systems.

A planet's axial tilt causes an Earth-bound observer to see varying views as the planet travels around the Sun. Uranus has a tilt of 98°, so it presents extreme changes in viewing geometry during its 84-year orbit. The Voyager 2 encounter with Uranus in 1986 occurred near that planet's southern summer solstice, with its south pole pointed almost directly toward the Sun, so the rings were face-on and fully illuminated as Voyager approached (*1*). Twice during a uranian year, the rings appear edge-on for a brief period, referred to as a ring plane crossing (RPX). We are currently in the midst of the first RPX since the rings were discovered in 1977 (Fig. 1) (*2*).

The RPX offers a rare opportunity to study features not usually observable, as exemplified by Saturn's RPX in 1995 (*3*–*5*). In particular, observations of the "dark" or unlit side of the rings—when Sun and Earth are on opposite sides of the ring plane—provide the chance to characterize faint, optically thin regions. As the rings' opening angle B decreases, optically thin rings brighten as $1/\sin(B)$, whereas optically thick rings fade as a result of mutual shadowing and obscuration of particles.

On 28 May 2007 (universal time), we obtained an infrared image of the dark side of the ring system with the 10-m W. M. Keck II telescope. We used the near-infrared camera NIRC2, coupled to the adaptive optics (AO) system. Thirty 1-min images were combined. The pixel size was ~146 km (0.01"), yielding an effective resolution of 660 km. Absolute photometry was bootstrapped from Uranus itself, with data obtained in July 2004 (*6*, *7*). Methane and hydrogen gas absorb sunlight in the K' band (2.2 μm), so Uranus is relatively dark, allowing

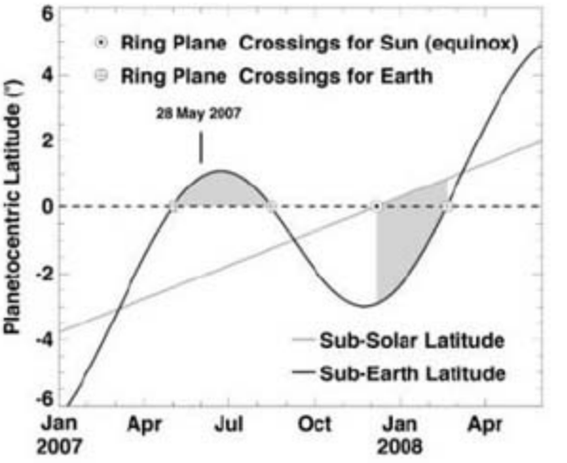

Fig. 1. Uranus-centered latitude of Earth and Sun during 2007 and early 2008. Earth crosses the ring plane three times: 3 May 2007, 16 August 2007, and 20 February 2008. The Sun crosses the ring plane on 7 December 2007 (equinox). Shaded regions indicate the times when Earth and Sun are on opposite sides of the ring plane (i.e., on opposite sides of 0° latitude), providing a rare Earth-based look at the unlit side of the rings. The date of our image is indicated.

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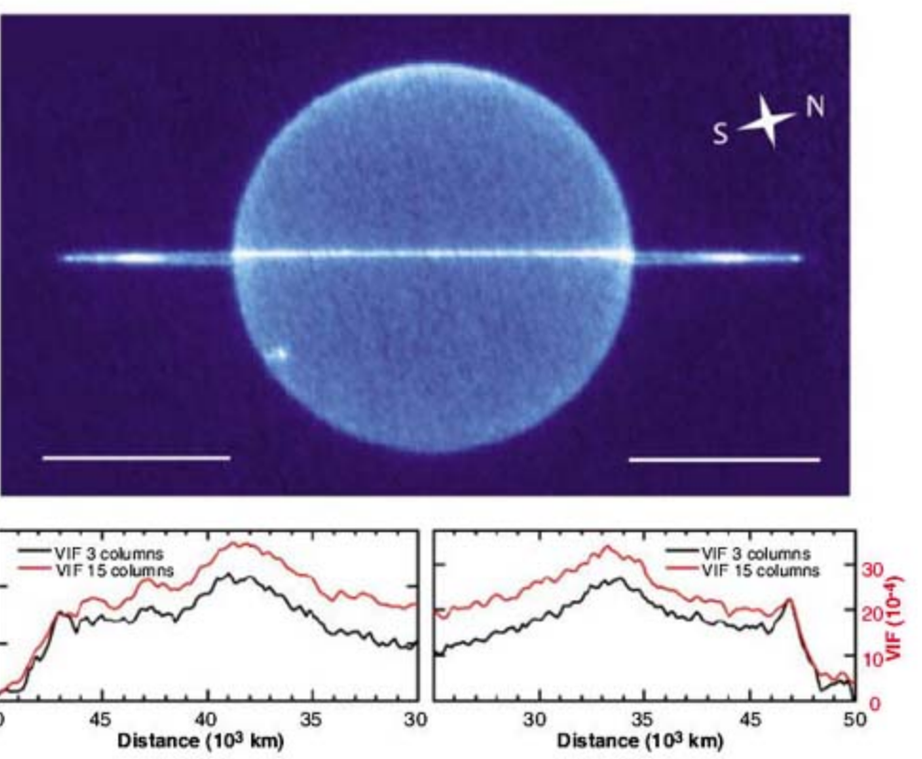

Fig. 2. The dark side of the rings of Uranus, as imaged by Keck AO. The image is rotated ~90°, so the ring plane is oriented horizontally, and celestial north points toward the right (as indicated by the compass rose). Below the figure are profiles of ring intensity versus projected radial distance. Horizontal white bars in the image indicate the approximate radial extent of these profiles. Two versions of each profile are shown: one integrated over three pixels normal to the ring plane (i.e., three columns in the image before rotation; black line) and the other over 15 pixels (red line). The broader integral captures more of the rings' light but shows somewhat less detail. The y axis is "VIF" or vertically integrated I/F. Here, I/F is a dimensionless quantity, where I is intensity and πF is the solar flux density. Note that the scales for VIF differ for the two integrals, with the black profile's scale shown at left and the red profile's scale shown at right.

ring material to be traced very close to the planet (Fig. 2). We did not detect the recently discovered outer ring system (*8*, *9*) because of the relatively short exposure time.

The rings show substantial changes from the lit side (Fig. 3). The ε ring's pericenter was oriented near the northern tip or "ansa" in all three epochs. The ε ring is narrowest at pericenter, so its smaller area results in a brightness minimum. This allows easier characterization of the (much fainter) inner rings. Because the ε ring's southern tip was ~2.5 times as bright as in 2004, and 4 times as bright as in 2006 (*6*), we focus our discussion here on the northern tip of the rings.

The radial extent of the rings appears much smaller in 2007. The ε ring, the dominant feature in observations before 2006 (*7*–*13*), is completely absent. This ring had begun to fade in 2006 (Fig. 3). In May 2007, the brightest part of the ring system is a feature referred to as the ζ ring (*14*). It has remained ambiguous whether this feature is related to the faint band of dust, R/1986 U 2, which was seen in a single Voyager image. The ring system is also exceptionally bright near ring η, which was already the brightest region on the northern ansa in 2006 (Fig. 3).

Radial scans through the images (Fig. 3) show that the ε ring has been fading rapidly year by year (Fig. 4A). The ζ ring, on the other hand, increased in brightness by a factor of ~2.5 between 2004 and 2006, as is expected for an optically thin ring. Overall, most rings interior to ε brightened between 2004 and 2006, though only by a factor of ~1.5 at most (*6*). Our 2007 profile differs markedly. On the unlit side of the optically thick main rings (4, 5, 6, α, β, η, γ, δ, and ε), the only detectable light is that which either gets transmitted through from the lit side or is reflected from the ring's edge. Thus, these rings essentially disappear, and the reflectivity will be dominated by light scattered through optically thin regions of the system.

A detailed comparison of the profiles (Fig. 4A), however, is complicated by the fact that the 2007 profile is edge-on, so all the rings are superposed atop each other. To extract the radial distribution from these scans, we have applied an "onion-peel" deconvolution to the 15-pixel-wide scans (Fig. 2, red profiles). This technique has been successfully applied to a variety of rings in the past (*5*, *15*, *16*). Starting from the outer edge, the intensity of the outermost zone is determined and subtracted from the entire scan, after which the intensity of the next zone inward is determined, and so on.

The deconvolved profile from 2007 (Fig. 4B) is compared with the 2004 data and a much finer resolution profile obtained by Voyager (*6*). This backscattered geometry emphasizes the larger (>1-cm) bodies within the system. We describe lighting geometry by the phase angle ϕ, the Sun-target-observer angle, which is near zero for all Earth-based observations. The profile from 2004 is a close match to the Voyager data, except for its coarser resolution. The 2007 profile, however, looks very different. The brightest feature is now ring η, followed closely by the broad, inner ring ζ.

Our observations probe optically thin sheets of material. Elsewhere in the solar system, optically thin rings are almost always dominated by micron-sized dust, so we may be seeing faint dust clouds surrounding the main rings of Uranus. Dust can be distinguished from larger bodies because it is strongly forward scattering. When Voyager passed Uranus and looked back toward the Sun (high ϕ), extensive lanes of dust were seen throughout the system (Fig. 4C). One other image taken near Voyager's RPX detected a faint, interior ring R/1986 U 2.

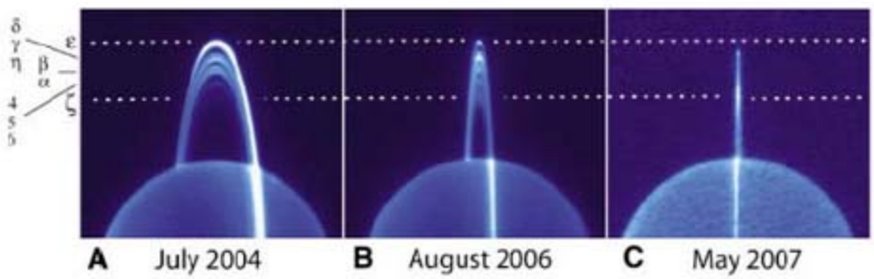

Fig. 3. Comparison of the lit and unlit sides of the rings of Uranus. (**A**) The lit side in early July 2004, when the angle B to Earth = 11° and the ring opening angle B_o to the Sun = 13.2° (*5*). (**B**) The lit side on 1 August 2006 when B = 3.6° and B_o = 5.2°. (**C**) The unlit side on 28 May 2007 when B = 0.7° and B_o = 2.0°. The dotted lines show the position of rings ε (top line) and ζ (bottom line). The pericenter of ε was near the tip of the ring in 2006, was at about the eleven o'clock position in 2004, and was at about the two o'clock position in 2007.

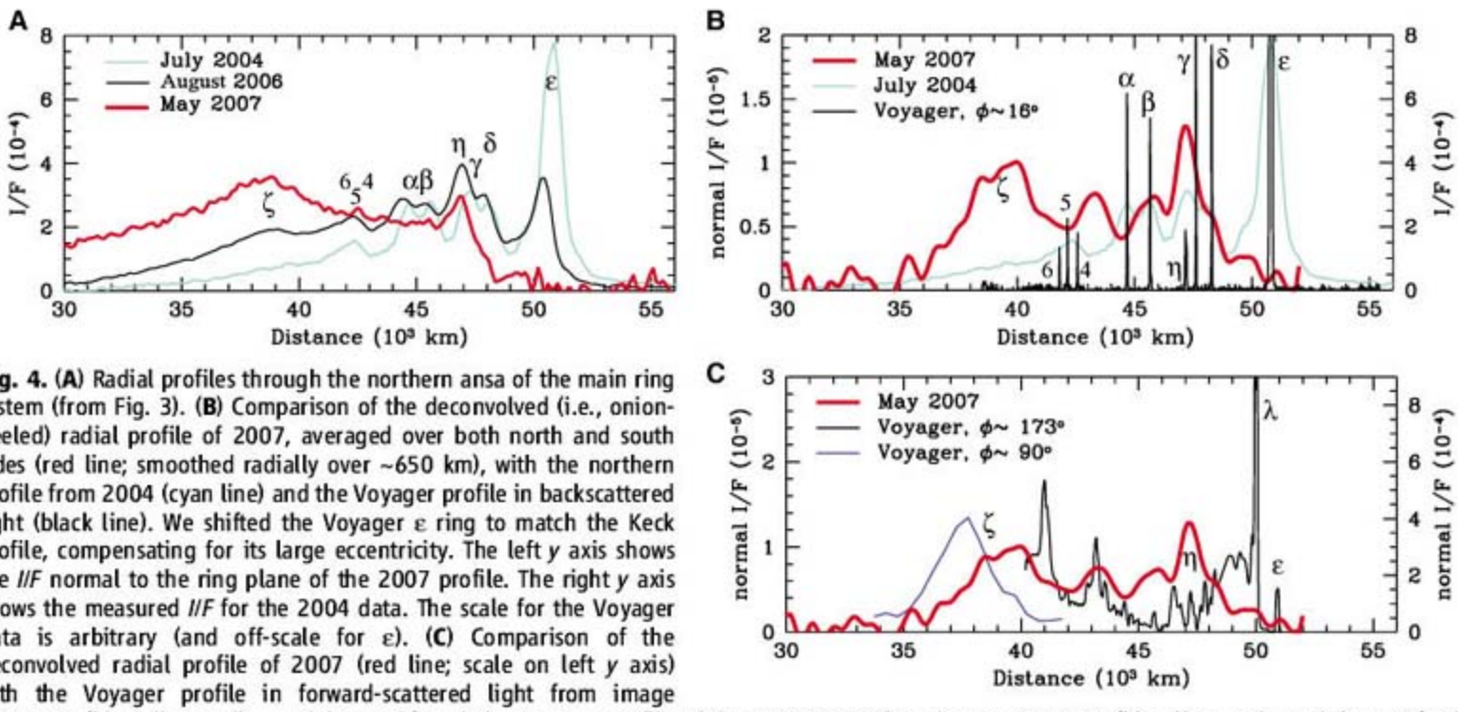

Fig. 4. (**A**) Radial profiles through the northern ansa of the main ring system (from Fig. 3). (**B**) Comparison of the deconvolved (i.e., onion-peeled) radial profile of 2007, averaged over both north and south sides (red line; smoothed radially over ~650 km), with the northern profile from 2004 (cyan line) and the Voyager profile in backscattered light (black line). We shifted the Voyager ε ring to match the Keck profile, compensating for its large eccentricity. The left y axis shows the I/F normal to the ring plane of the 2007 profile. The right y axis shows the measured I/F for the 2004 data. The scale for the Voyager data is arbitrary (and off-scale for ε). (**C**) Comparison of the deconvolved radial profile of 2007 (red line; scale on left y axis) with the Voyager profile in forward-scattered light from image 26852.19 (black line; scale on right y axis) and the Voyager profile of the R/1986 U 2 from image 26846.50 (blue line; scale on left y axis). The Voyager data were smoothed to match the Keck pixel size.

The Voyager profiles (Fig. 4, B and C) look very different from ours, but a few features clearly correspond to known rings. Stellar occultations have revealed that two uranian rings have broad, optically thin components (*17*): Ring η has a 55-km outward extension and ring δ has a 12-km inward extension. The η ring's extension provides a natural explanation for its rapid growth in brightness as B decreases. Furthermore, Fig. 4C shows a subtle inflection closely aligned with ring δ, suggesting that its optically thin companion is glowing brighter at small B. Ring λ illustrates how a dusty ring should appear in our data (Fig. 4C). It is visible but at a level about 150 times as faint as that in the high-phase Voyager image. Such a ratio is compatible with the typical light-scattering properties of micron-sized dust. A broad feature at 43,000 km (from the center of Uranus) could also be related to dust seen by Voyager, but this feature remains somewhat ambiguous in our data because it was only detected on the south ansa (Fig. 2).

Many of the other ring components are difficult to reconcile with known rings. If such features are long-term members of the system, then they somehow escaped detection. Consider the region near 45,000 km, which is nearly devoid of dust according to Voyager but is about half as bright as the η ring in our profile. One can devise an optically thin, backscattering population that fits the data, but extensive imaging by Voyager revealed no such population.

Even stranger is the ζ ring, which shifted radially from the Voyager epoch to the present. Because of the different phase angles, one cannot make any conclusive inferences about the particle sizes. Nevertheless, we require a broad, backscattering population centered at 40,000 km from the center of Uranus and an overlapping, slightly less backscattering population shifted inward by several thousand kilometers. Such an explanation seems rather ad hoc, and it is difficult to understand how particles of slightly different sizes and scattering properties could become spatially segregated.

A simpler alternative is that the faint material we see is indeed dust but that its radial distribution has changed since 1986, in fact much more dramatically than was suggested a year ago (*7*). One usually assumes that ring systems are static, but we now have several counterexamples. At Saturn, the D ring has changed substantially from the Voyager epoch (1980–1981) to the present (*18*), and the F ring also shows numerous changes (*19*). At Neptune, the pattern of dusty arcs in the Adams ring is very different now as compared with that from Voyager's first images in 1989 (*20*, *21*). We conclude that changes in dusty rings over ~20-year time scales are common. The changes seen in Uranus' ring system, however, are much larger in scale than anything seen previously.

Changes over year-to-decade time scales are dynamically plausible because the dust populations that we see represent extremely tiny amounts of material, and the orbits of small dust grains evolve rapidly in response to nongravitational forces (e.g., Poynting-Robertson and plasma drag, Lorentz forces) (*22*). The rings were once expected to represent a steady state between dust creation and removal processes. However, we now realize that these states are far from steady and may be dominated by infrequent events, such as large impacts, that inject highly visible quantities of dust, as has been discussed for Saturn's A ring (*23*).

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Probing Quantum Commutation Rules by Addition and Subtraction of Single Photons to/from a Light Field

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The possibility of arbitrarily "adding" and "subtracting" single photons to and from a light field may give access to a complete engineering of quantum states and to fundamental quantum phenomena. We experimentally implemented simple alternated sequences of photon creation and annihilation on a thermal field and used quantum tomography to verify the peculiar character of the resulting light states. In particular, as the final states depend on the order in which the two actions are performed, we directly observed the noncommutativity of the creation and annihilation operators, one of the cardinal concepts of quantum mechanics, at the basis of the quantum behavior of light. These results represent a step toward the full quantum control of a field and may provide new resources for quantum information protocols.

Classically, the operation of deterministically adding an object to an ensemble and then subtracting another leaves the statistics unaltered, as long as all the objects are identical. The probability distribution would just shift by one unit toward larger values when one object is added and then shift back to its initial position when another is extracted. For an ensemble of identical quantum particles, however, the situation may be different. For example, if the particles were photons in a single-mode radiation field, one would naturally use the bosonic creation and annihilation operators $\hat{a}^{\dagger}$ and $\hat{a}$ to perform the addition and the subtraction of single photons to and from the light field. Indeed, for the general case of a quantum light field described by

a density matrix $\hat{\rho}$, there is a broad consensus in calling the result of the application of the creation (annihilation) operator, $\hat{a}^\dagger\hat{\rho}\hat{a}$ ($\hat{a}\hat{\rho}\hat{a}^\dagger$), the "photon-added" ("-subtracted") state, after proper normalization. This tendency derives from the fact that, when the photon creation operator $\hat{a}^\dagger$ acts on a state with a well-defined number n of photons (also called a Fock or number state, and denoted by $|n\rangle$), it increases this number by one:

$$\hat{a}^\dagger|n\rangle = \sqrt{n+1}|n+1\rangle. \quad (1)$$

Conversely, when the photon annihilation operator $\hat{a}$ acts on the same state, it subtracts a quantum of excitation, thus reducing the number of photons in the state by exactly one (*1*, *2*):

$$\hat{a}|n\rangle = \sqrt{n}|n-1\rangle. \quad (2)$$

When the initial number of particles is precisely known, the quantum and the classical cases give exactly the same results for arbitrary sequences of additions and subtractions. However, the situation changes completely for general superpositions or mixtures of Fock states. After the operation of particle subtraction, the average number of quantum particles in certain states may unexpectedly grow instead of diminishing, as one would be naturally tempted to expect (*2*). Furthermore, adding one particle to the system by a creation operator and then, immediately after, subtracting another by an annihilation operator would lead to a final probability distribution of the ensemble completely different from the initial one. Although counterintuitive, this behavior is not unphysical and does not put energy conservation at stake: It simply derives from the misleading implicit assumption that a deterministic addition and subtraction of particles can be represented by the creation and annihilation operators which, on the contrary, work in a probabilistic way.

For light, it is straightforward to show that the operation of photon addition always produces a nonclassical light state (*3*–*6*), whereas photon subtraction gives a final nonclassical field only if the original one was already nonclassical (*7*, *8*). Apart from the particular case of Fock states, and in an apparent contrast to the classical situation, the sequence of photon creation and annihilation always creates a state different from the original one. Furthermore, due to the noncommutativity of $\hat{a}^\dagger$ and $\hat{a}$ (i.e., $[\hat{a}, \hat{a}^\dagger] \neq 0$), the reverse sequence of operators is expected to produce another state that is different from both, as $\hat{a}\hat{a}^\dagger \neq \hat{a}^\dagger\hat{a} \neq \mathbf{1}$.

A thermal state is the most classical state of light, formed by a statistical mixture of coherent states. Its density matrix is diagonal in the Fock state basis and, accordingly, exhibits no phase dependence. It can thus be completely described in terms of its photon number distribution. The addition and subtraction of a single photon from the spatiotemporal mode containing the thermal light state can be performed in a conditional way, that is, by producing the target photon-added or -subtracted state only upon the positive outcome of a separate measurement. In particular, the controlled addition of a single photon can be realized by the conditional stimulated parametric down-conversion in a nonlinear optical crystal (*3*–*5*). When an ultraviolet pump photon interacts in the crystal, it may spontaneously decay into two quantum-mechanically entangled infrared (IR) photons traveling along different directions (conserving the total momentum) and with energies that sum up to that of the parent photon. When one of the two IR photons (the so-called trigger photon) is detected along a particular direction with a given energy, the spatial properties and the energy of the other are also unambiguously determined. If one injects a seed light field into the crystal, then stimulated emission may occur into the same mode, and the detection of the trigger photon now indicates the conditional generation of the photon-added seed state in a well-defined spatiotemporal mode.

The implementation of photon subtraction implies the controlled reflection of a single photon off the right mode by a beam splitter (*7*). A "click" in an on/off photodetector placed in the reflected path indicates the successful subtraction of a single photon from the input field. It can be explicitly proven that the above procedures for conditional single-photon addition and subtraction from a light field are faithful implementations of the photon creation and annihilation operators $\hat{a}^\dagger$ and $\hat{a}$ for sufficiently low crystal parametric gain and beam-splitter reflectivity (*2*). Combining single-photon addition and subtraction by such methods constitutes a much harder experimental challenge because it requires a perfect matching of all the involved field modes and implies a double conditioning, with a much lower success rate, to prepare the final light state.

To perform the two operations in two separate sequences, we have combined three different modules, each implementing the action of a specific

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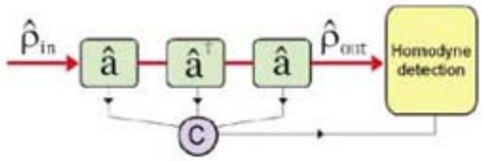

Fig. 1. Schematic of the sequence of modules representing specific quantum operators acting on a quantum light field (denoted by its density matrix $\hat{\rho}_{in}$). A module for single-photon creation (denoted by $\hat{a}^\dagger$) is placed between two modules for single-photon annihilation (denoted by $\hat{a}$). The final state $\hat{\rho}_{out}$ is conditionally prepared and analyzed by the homodyne detector whenever a specific sequence of "clicks" arrives from the modules and is passed on by the logic circuit (C). Single-click events herald the production of a "photon-added" or "photon-subtracted" state. Double-click events herald the production of a quantum state that has undergone the sequence of photon addition and subtraction or vice versa. Double photon-subtraction events are not considered in the present experiment.

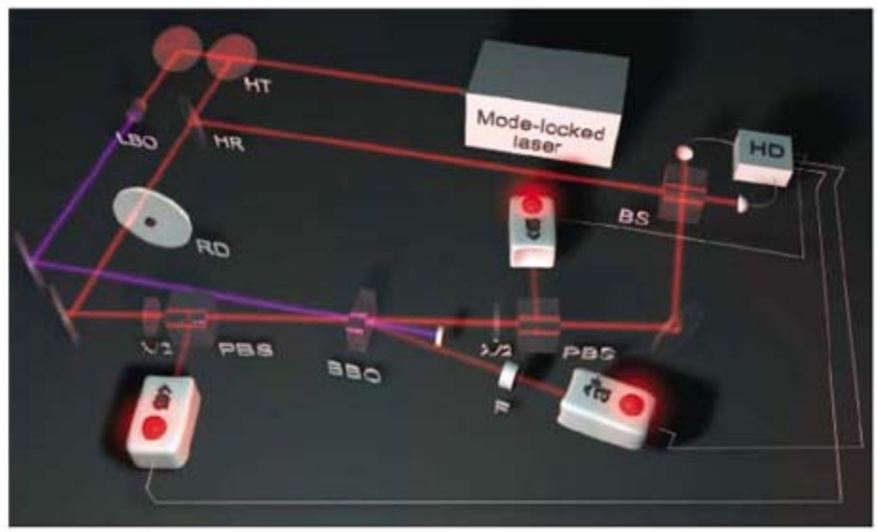

Fig. 2. Experimental setup. Pulses at a wavelength of 786 nm are emitted at a repetition rate of 82 MHz from a mode-locked picosecond Ti:sapphire laser. They are split by a high-transmission (HT) and a high-reflectivity (HR) beam splitter to serve as (i) the pump for parametric down-conversion in a 3-mm-thick, type-I beta-barium borate (BBO) crystal after frequency-doubling in a lithium triborate (LBO) crystal; (ii) the seed thermal field, after scattering off a rotating ground glass disk (RD) and spatial cleaning by a single-mode optical fiber (not shown); and (iii) the local oscillator field for balanced homodyne detection (HD) after mixing with the investigated states in a 50% beam splitter (BS). F is a combination of spectral and spatial filters made of a pair of etalon interference filters with a narrow (50 GHz) spectral width, and a single-mode optical fiber directly connected to an on/off photodetector (Perkin-Elmer SPCM AQR-14, denoted by $\hat{a}^\dagger$). Pairs of half-wave plates ($\lambda/2$) and polarizing beam splitters (PBS) serve to implement the photon-subtraction modules together with fiber-coupled on/off photodetectors (denoted by $\hat{a}$).

quantum operator on the light state (Fig. 1). Two combinations of half-wave plates and polarizing beam splitters, together with on/off photodetectors in the reflected channel, form the photon-subtraction modules that are placed in the path of the thermal light field, respectively before and after the parametric crystal that, with the on/off photodetector in the trigger channel, forms the photon-addition module. By rotating the two half-wave plates, we can control the beam-splitter reflectivities to alternately switch off one or both of the subtraction modules. Then, by choosing the right combination of clicks coming from the module detectors, we can select the desired quantum operation, or any sequence of them. A single click simply conditions the generation of a photon-added or photon-subtracted thermal state, whereas a double click can either produce a first-subtracted-then-added thermal state or vice versa, depending on the combination of clicks. We use a synchronized, ultrafast, time-domain, balanced homodyne detector (*9*) to analyze the conditionally prepared states by repeatedly measuring their electric field quadratures and building up quadrature distributions. The reference field (usually named "local oscillator") for the homodyne measurements comes from the same picosecond pulsed laser, which provides the thermal seed field and, once frequency-doubled, the pump pulses for the parametric crystal (Fig. 2). As the generated states are, by construction, phase independent, we have acquired about 10^5 quadrature measurements per state, leaving the phase of the local oscillator unlocked. As the combined action of addition and subtraction is rather rare (with only about 10 double-click events every second), a full quadrature distribution may take up to 5 hours to acquire in such cases.

We have first measured the unperturbed thermal light field, then the state resulting from single-photon addition, single-photon subtraction, and from both the addition-subtraction and subtraction-addition sequences. Figure 3 shows the experimental quadrature distributions for all the states obtained from an initial thermal distribution with $\bar{n} = 0.57$, together with the curves calculated while keeping all experimental inefficiencies into account (*2*). Next to them, the corresponding photon number probability distributions are plotted as theoretically calculated and as reconstructed from the experimental data by means of an iterative maximum likelihood algorithm (*10*–*12*), correcting for the finite detection efficiency (*2*).

The first interesting result appears when comparing the mean photon numbers of the states: For the photon-added state one finds, quite naturally, that the mean photon number is larger than in the original thermal light state, but unexpectedly the same result occurs for the photon-subtracted state. The operation of removing one photon from the field has increased (doubled) its final mean photon number. Such an increase also takes place for the sequence of operators that should intuitively bring the field back to the initial state.

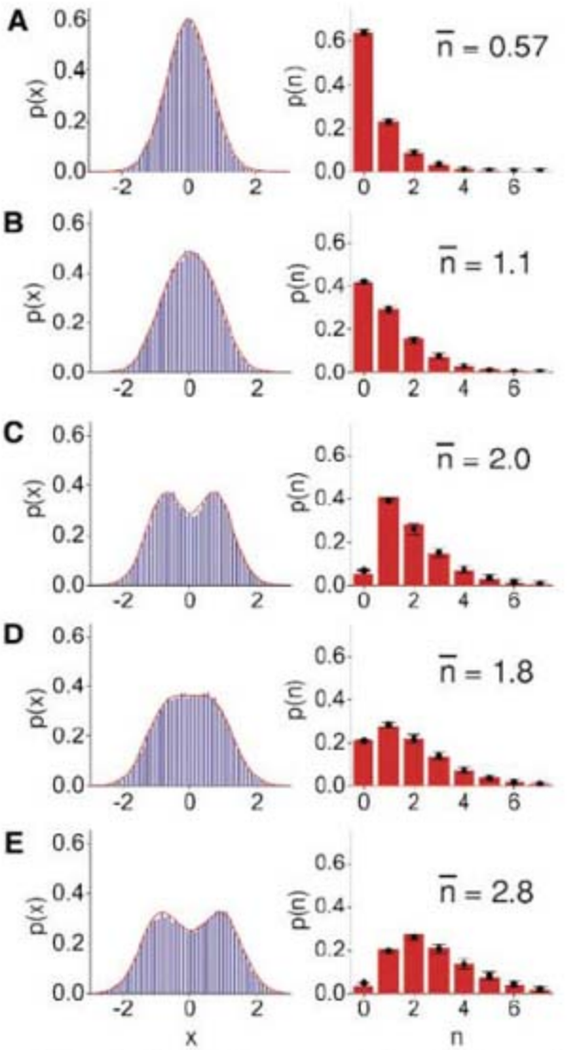

Fig. 3. Experimental quadrature distribution histograms and theoretical curves (superposed solid lines) for **(A)** the original thermal state; **(B)** the photon-subtracted state; **(C)** the photon-added state; **(D)** the photon-added-then-subtracted state; **(E)** the photon-subtracted-then-added state. The second column shows the corresponding theoretical (red bars) and experimentally reconstructed (solid circles with error bars) photon number distributions. States resulting from a final photon addition present a very small vacuum contribution, which makes them highly nonclassical. The residual vacuum term derives from imperfections in the preparation of the states and is satisfactorily accounted for by the theoretical model (*2*). The mean photon number in the state is also shown as calculated from the reconstructed distributions.

The experimentally reconstructed density matrix elements for the states have then been used to obtain their corresponding Wigner functions (WFs) (*13*). Quasi-probability distributions fully describe the state of a quantum system in phase-space (the space spanned by two orthogonal quadratures of the electromagnetic field for a single-mode state of light, as in this case) in the same manner as a positive-definite probability distribution characterizes a classical system. The negativity of the WF is indeed a good indication of the highly nonclassical character of the state.

A clear negativity of the reconstructed WFs (which survives even without correcting for detection losses) is obtained in all the cases where photon addition is the last operator acting on the states, thus showing their high degree of nonclassicality. However, the WFs of states resulting from the two sequences of addition and subtraction show other interesting features (Fig. 4). The two final states are different from each other and from the original thermal state. In both cases, the WF exhibits a clear central dip, which is absent in the WF of the thermal field; such a dip reaches negative values for the subtract-then-add sequence, whereas it stays well in the positive region for the add-then-subtract sequence (*14*). This provides a direct experimental verification of the noncommutativity of the quantum bosonic creation and annihilation operators and gives a visually convincing demonstration that a simple view of classical particle addition and subtraction is incorrect in this case. The noncommutativity of bosonic annihilation and creation operators is at the basis of many "weird" quantum phenomena of light. The mere existence of a vacuum field (with spontaneous emission, the Lamb shift, or the Casimir effect as some of its main manifestations) is a direct consequence of this. Furthermore, the difference in the resulting states obtained by applying noncommuting quantum operators in re-

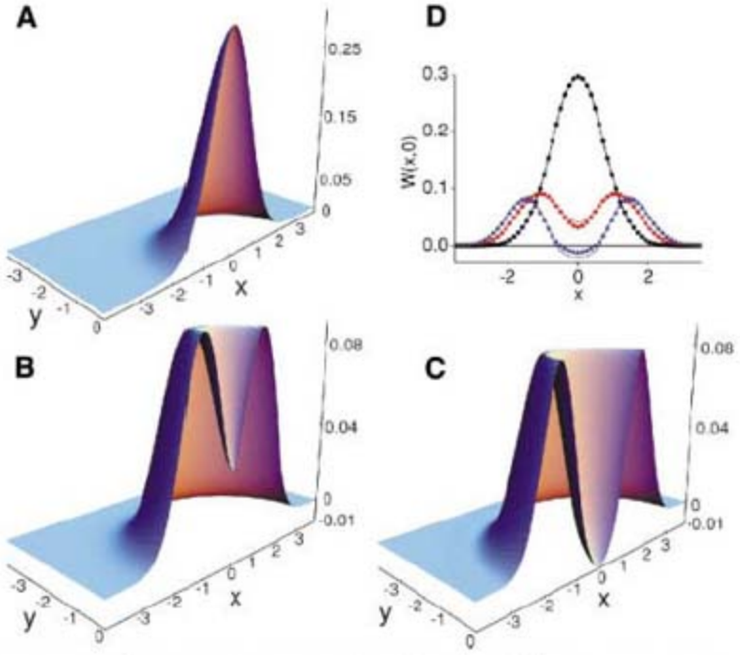

Fig. 4. Experimental WFs (corrected for detection inefficiency) for **(A)** the original thermal state; **(B)** the photon-added-then-subtracted state; **(C)** the photon-subtracted-then-added state. **(D)** presents sections of the above Wigner functions (black squares correspond to the thermal field; red circles and blue triangles correspond to the photon-added-then-subtracted and the photon-subtracted-then-added states, respectively), together with the corresponding theoretical predictions (solid curves) (*2*).

verse order, as in this case, is the real essence of the Heisenberg uncertainty principle. Besides its fundamental importance, the experimental implementation of such a sequence of basic quantum operations is an essential tool for the full-scale engineering of a quantum light state optimized for a multitude of different tasks (*15*), including robust quantum communication. As any quantum operation, including non-Gaussian operations, is composed of photon additions and subtractions (i.e, it can be expressed as $f(\hat{a},\hat{a}^{\dagger})$), our experimental results constitute a step toward the full quantum control of a field and the generation of highly entangled states (*16*).

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Symmetrized Characterization of Noisy Quantum Processes

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A major goal of developing high-precision control of many-body quantum systems is to realize their potential as quantum computers. A substantial obstacle to this is the extreme fragility of quantum systems to "decoherence" from environmental noise and other control limitations. Although quantum computation is possible if the noise affecting the quantum system satisfies certain conditions, existing methods for noise characterization are intractable for present multibody systems. We introduce a technique based on symmetrization that enables direct experimental measurement of some key properties of the decoherence affecting a quantum system. Our method reduces the number of experiments required from exponential to polynomial in the number of subsystems. The technique is demonstrated for the optimization of control over nuclear spins in the solid state.

Quantum information enables efficient solutions to certain tasks that have no known efficient solution in the classical world, and it has reshaped our understanding of computational complexity. Harnessing the advantages of the quantum world requires the ability to robustly control quantum systems and, in particular, counteract the noise and decoherence affecting any physical realization of quantum information processors (QIPs). A pivotal step in this direction came with the discovery of quantum error correction codes (QECCs) (*1*, *2*) and the threshold theorem for fault-tolerant (FT) quantum computation (*3*–*6*). To make use of quantum error correction and produce fault-tolerant protocols, we need to understand the nature of the noise affecting the system at hand. There is a direct way to fully characterize the noise using a procedure known as process tomography (*7*–*9*). However, this procedure requires resources that grow exponentially with the number of subsystems (usually two-level systems called "qubits") and is intractable for characterizing the multi-qubit quantum systems that are presently realized

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(*10*–*12*). We introduce a general symmetrization method that allows for direct experimental characterization of some physically relevant features of the decoherence and apply it to develop an efficient experimental protocol for measuring multiqubit correlations and memory effects in the noise. Compared with existing methods (*13*), the protocol yields an exponential savings in the number of experiments required to obtain such information. In the context of applications, this information enables optimization of error-correction strategy and tests of some assumptions underlying estimates of the FT threshold. Moreover, the estimated parameters are immediately relevant for optimizing experimental control methods.

Focusing on a system of n qubits, a complete description of a general noise model Λ requires $O(2^{4n})$ parameters. Clearly an appropriate coarse-graining of this information is required; the challenge is to identify efficient methods for estimating the features of practical interest. The method we propose is based on identifying a symmetry associated with a property of interest, and then operationally symmetrizing the noise to yield an effective map $\overline{\Lambda}$, with a reduced number of independent parameters reflecting these properties (Fig. 1). This symmetrization is achieved by conjugating the noise (Fig. 2) with a unitary operator drawn randomly from the relevant symmetry group and then averaging over these random trials (*14*–*18*). We show below that rigorous statistical bounds guarantee that the number of experimental trials required is independent of the dimension of the group. Hence, our randomization method leads to efficient partial characterization of the map Λ whenever the group elements admit efficient circuit decompositions.

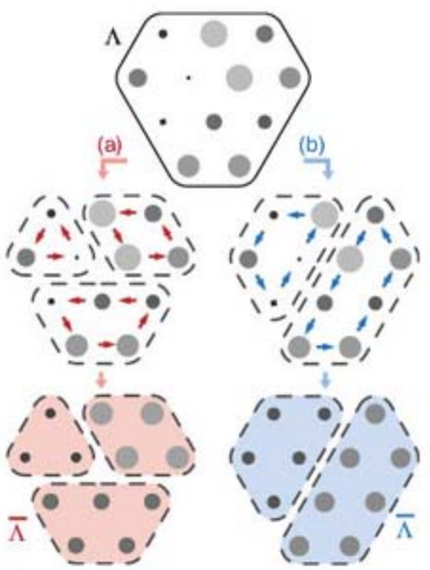

Fig. 1. Schematic of coarse-graining by symmetrization. Averaging the noise Λ by twirling under a symmetry group yields an effective noise process that has a reduced number of independent parameters. Distinct symmetrization groups [represented by (a) red and (b) blue] uniformize different subsets of parameters.

We apply this general idea to the important problem of estimating the noise parameters that determine the performance of a broad class of QECCs and the applicability of certain assumptions underlying FT thresholds. In general, QECCs protect quantum information only against certain types of noise. A distance-$(2t + 1)$ code refers to codes that correct all errors simultaneously, affecting up to t qubits. Hence, the distance of a QECC determines which terms in the noise will be corrected and which will remain uncorrected. The latter contribute to the overall failure probability. To estimate the failure probability, many fault-tolerance theorems assume that the noise is independent from qubit to qubit or between blocks of qubits. Another common assumption is that the noise is memoryless and hence Markovian in time. Our protocol enables measurements of these noise correlations under a given experimental arrangement without the exponential overhead of process tomography. This protocol is efficient also in the context of an ensemble QIP with highly mixed states (*19*).

We start by expanding the noise operators in the basis $P_i \in P_n$, consisting of n-fold tensor product of the usual single-qubit Pauli operators $\{1, X, Y, Z\}$ satisfying the orthogonality relation $\mathrm{Tr}[P_i\ P_j] = 2^n\ \delta_{ij}$. The Clifford group $\mathcal{C}_n$ is defined as the normalizer of the Pauli group $\mathcal{P}_n$: it consists of all elements U_i of the unitary group $U(2^n)$ satisfying $U_i P_j U_i^{\dagger} \in \mathcal{P}_n$ for every $P_j \in \mathcal{P}_n$. The protocol requires symmetrizing the channel $\Lambda \rightarrow \overline{\Lambda}$ by averaging over trials in which the channel is conjugated by the elements of $\mathcal{C}_1$ applied independently to each qubit (Fig. 2). An average over conjugations is known as a "twirl" (*20*), and we call the above a $\mathcal{C}_1^{\otimes n}$-twirl.

Separating out terms according to their Pauli weight w, where $w \in \{0,...,n\}$ is the number of nonidentity factors in P_i, letting the index $\nu_w \in \{1, ..., \binom{n}{w}\}$ count the number of distinct ways that w nonidentity Pauli operators can be distributed over the n factor spaces, and the index $\mathbf{i}_w = \{i_1, ..., i_w\}$ with $i_j \in \{1, 2, 3\}$ denote which of the nonidentity Pauli operators occupies the j^{th} occupied site, we obtain (see SOM text)

$$\overline{\Lambda(\rho)} = \sum_{w=0}^{n} \sum_{\nu_w=1}^{\binom{n}{w}} r_{w,\nu_w} \sum_{\mathbf{i}_w} P_{w,\nu_w,\mathbf{i}_w}\, \rho\, P_{w,\nu_w,\mathbf{i}_w} \tag{1}$$

where the reduced parameters $r_{w,\nu w}$ are fixed by Λ and $p_w = 3^w \sum_{\nu_w=1}^{\binom{n}{w}} r_{w,\nu w}$ are the probabilities of w simultaneous qubit errors in the noise. Some intuition about how a $\mathcal{C}_1^{\otimes n}$-twirl simplifies the task of noise characterization is obtained by analyzing the case of a single qubit (SOM text).

To measure these probabilities, we probe $\overline{\Lambda}$ with input state $|0\rangle \equiv |\ 0\rangle^{\otimes n}$, followed by a projective measurement of the output state in the basis $|l\rangle$. This yields an n-bit string $l \in \{0, 1\}^n$. Let q_w denote the probability that a random subset of w bits of the binary string l has even parity. This gives the eigenvalues of $\overline{\Lambda}$ as $c_w \equiv \langle \overline{Z^{\otimes w}} \rangle = 2q_w - 1$, and we obtain $p_{w'} = \sum_w \Omega^{-1}_{w',w} c_w$,

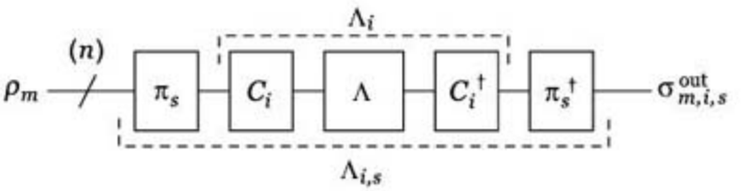

Fig. 2. Quantum circuit. One experimental run consists of a conjugation of the noise process Λ. The standard protocol requires conjugation only by an element C_i, whereas the ensemble protocol requires conjugating Λ also by a permutation π_s of the qubits. The standard protocol requires only one input state $|\ 0\rangle^{\otimes n}$, whereas the ensemble protocol requires n distinct input operators ρ_w.

Table 1. Summary of experimental results. The first four sets of experiments (three sets on the two-qubit liquid-state system and one on the three-qubit solid-state system) were designed to characterize the performance of the protocol under engineered noise. The final two sets demonstrate characterization of the (unknown) natural noise affecting the quantum memory created by multiple-pulse time-suspension sequences with different pulse spacings.

No.	System	Map description	Kraus operators (A_k)	k	p_0	p_1	p_2	p_3
1	$CHCl_3$	Engineered: $\mathbf{p} = [0,1,0]$.	$\frac{1}{\sqrt{2}}\{Z_1, Z_2\}$	288	$0.000^{+0.004}$	$0.991^{+0.009}_{-0.015}$	$0.009^{+0.017}_{-0.009}$	-
2	$CHCl_3$	Engineered: $\mathbf{p} = [0,0,1]$.	$\{Z_1\ Z_2\}$	288	$0.001^{+0.006}_{-0.001}$	$0.004^{+0.011}_{-0.004}$	$0.996^{+0.004}_{-0.011}$	-
3	$CHCl_3$	Engineered: $\mathbf{p} = [\frac{1}{4},\frac{1}{2},\frac{1}{4}]$.	$\{\exp[i\frac{\pi}{4}(Z_1 + Z_2)]\}$	288	$0.254^{+0.010}_{-0.010}$	$0.495^{+0.021}_{-0.020}$	$0.250^{+0.019}_{-0.019}$	-
4	$C_3H_4O_4$	Engineered: $\mathbf{p} = [0,1,0,0]$.	$\frac{1}{\sqrt{3}}\{Z_1, Z_2, Z_3\}$	432	$0.01^{+0.01}_{-0.01}$	$0.99^{+0.01}_{-0.03}$	$0.01^{+0.02}_{-0.01}$	$0.00^{+0.01}$
5	$C_3H_4O_4$	Natural Noise (i)	unknown	432	$0.44^{+0.01}_{-0.02}$	$0.45^{+0.03}_{-0.03}$	$0.10^{+0.04}_{-0.08}$	$0.01^{+0.03}_{-0.01}$
6	$C_3H_4O_4$	Natural Noise (ii)	unknown	432	$0.84^{+0.01}_{-0.01}$	$0.15^{+0.02}_{-0.03}$	$0.01^{+0.03}_{-0.01}$	$0.00^{+0.02}$

where the matrix $\Omega^{-1}_{w',w}$ is a matrix of combinatorial factors (SOM text). If in each single-shot experiment, the Clifford operators are chosen uniformly at random, then with $K = O[\log(2n)/\delta^2]$ experiments we can estimate each of the coefficients c_w to precision δ with constant probability. All imperfections in the protocol contribute to the total probabilities of error. The protocol can be made robust against imperfections in the input state preparation, measurement, and twirling by factoring out the values $c_w(0)$ measured when the protocol is performed without the noisy channel: $c_w \rightarrow \tilde{c}_w = c_w/c_w(0)$.

The c_w can be applied directly to test some of the assumptions that affect estimates of the fault-tolerance threshold (*21*, *22*). In particular, a noisy channel with an uncorrelated distribution of error locations, but with arbitrary correlations in the error type, is mapped under our symmetrization to a channel that is a tensor product of n single-qubit depolarizing channels. A channel satisfying this property will exhibit the scaling $c_w = c_1^w$. Hence, observed deviations from this scaling imply a violation of the above assumption. However, there are correlated error models that also give rise to this scaling, so the converse implication does not hold.

Furthermore, we can test for non-Markovian properties by repeating the above scheme for distinct time intervals $m\tau$ with increasing m. If, over the time scale τ, the noise satisfies the Markovian semigroup property $\Lambda_\tau \circ \Lambda_\tau = \Lambda_{2\tau}$ (*23*), then so will the twirled map $\overline{\Lambda}_\tau \circ \overline{\Lambda}_\tau = \overline{\Lambda}_{2\tau}$. Consequently, the coefficients $c_w(m\tau)$ measured over the time-scale $m\tau$ will satisfy $c_w(m\tau) = c_w(\tau)^m$. Observed deviations from this scaling imply non-Markovian effects in the untwirled noise. However, again the converse does not hold; consistency with this scaling does not guarantee that the untwirled noise obeys the Markovian semigroup property.

When applying $\{c_w\}$ to estimate $\{p_w\}$, the statistical uncertainty for p_w grows exponentially with w (SOM text). This still allows for characterization of other important features of the noise. Specifically, the probability p_0 is directly related to the entanglement fidelity of the channel, so this protocol provides an exponential savings over recently proposed methods for estimating this single figure of merit (*16*, *24*, *25*). [For another approach, see (*17*)]. Hence, by actually implementing any given code, we can bound the failure probability of that code with only $O[\log(2n)/\delta^2]$ experiments and without making any theoretical assumptions about the noise. Moreover, on physical grounds, we may expect the noise to become independent between qubits outside some fixed (but unknown) scale b, after which the p_w decreases exponentially with w. The scale b can be determined efficiently with $O(n^b)$ experiments.

Although a characterization of the twirled channel is useful given the relevance of twirled channels in some fault-tolerant protocols (*22*), the failure probability of the twirled channel gives an upper bound to the failure probability of the original untwirled channel whenever the performance of the code has some bound that is invariant under the symmetry associated with the twirl. This holds quite generally in the context of the symmetry considered above because the failure probability of a generic distance-$(2t + 1)$ code is bounded above by the total probability of error terms with Pauli weight greater than t, and this weight remains invariant under conjugation by any $C_i \in \mathcal{C}_1^{\otimes n}$.

Our protocol is efficient also in the context of an ensemble QIP (*19*). We prepare deviations from the identity state of the form $\rho_w = Z^{\otimes w} \otimes 1^{\otimes(n-w)}$, with $w \in \{1, \ldots n\}$; hence, the (non-scalable) preparation of pseudo-pure states is avoided. As illustrated in Fig. 2, the ensemble protocol consists of conjugating the process $\Lambda \rightarrow \Lambda_{i,s}$ with a randomly chosen pair (C_i, π_s) in each run, where π_s is a random permutation of the qubits. For input operator ρ_w, the output is $\sigma^{\text{out}}_{w;i,s} = \Lambda_{i,s}(\rho_w)$. Averaging the output operators $\sigma^{\text{out}}_{w;i,s}$ over i and s returns the input operator scaled by c_w.

We performed an implementation of the above protocol on both a two-qubit (chloroform $CHCl_3$) liquid-state and a three-qubit (single-crystal Malonic acid $C_3H_4O_4$) solid-state nuclear magnetic resonance QIP (*26*). The results of these experiments are summarized in Table 1. Statistical analysis for one liquid-state set is shown in fig. S1 and for the final two solid-state sets in Fig. 3. The final two sets of (solid-state) experiments were performed to characterize the unknown residual noise occurring under (i) one cycle of a C48 pulse sequence (*27*) with 10 μs pulse spacing, and (ii) two cycles of C48 with 5 μs pulse spacing. The C48 sequence is designed to suppress the dynamics due to the system's internal Hamiltonian and could be used, for example, for quantum memory. The evolution of the system under this pulse sequence can be evaluated theoretically by calculating the Magnus expansion (*28*) of the associated effective Hamiltonian, under which the residual effects appear as a sum of terms associated with the Zeeman and dipolar parts of the Hamiltonian, including cross terms. Roughly speaking, effective suppression of the k^{th} term of the Hamiltonian takes places when $\gamma_k \tau_k \ll 1$, where γ_k is the strength of the term and τ_k^{-1} is the rate at which it is modulated by the pulse sequence. Generally, shorter delays lead to improved performance unless there is a competing process at the shorter time scale. Although two repetitions of the sequence with the pulse spacing of 5 μs has twice as many pulses as the single sequence with the 10 μs spacing, the probabilities of one-, two-, and three-body noise terms all decrease substantially (Table 1). However, the averaging under the 5 μs falls short of ideal performance as a result of incomplete (heteronuclear) decoupling of the qubits (three carbon nuclei) from the envi-

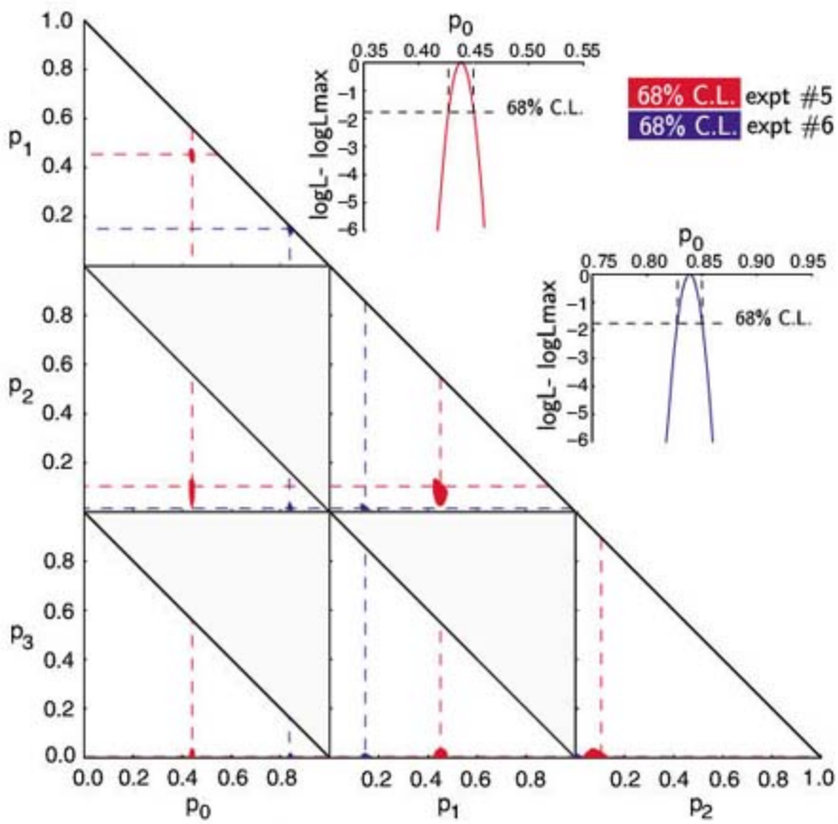

Fig. 3. Results for p_w from experiments 5 and 6 in Table 1. Shown are projections of the four-dimensional likelihood function onto various probability planes. The asymmetry seen in some of the confidence areas is a result of this projection. The results for one cycle with 10 μs pulse spacing (experiment 5) are in red, and the results for two cycles with 5 μs spacing (experiment 6) are in blue.

ronment (nearby hydrogen nuclei) (SOM text). For both sequences, the noise coefficients c_w do not statistically deviate from the scaling implied by uncorrelated errors (fig. S3), although, as noted above, this does not guarantee that the errors are uncorrelated.

Our method provides an efficient protocol for the characterization of noise in contexts where the target transformation is the identity operator, for example, a quantum communication channel or quantum memory. However, the protocol also provides an efficient means for characterizing the noise under the action of a nonidentity unitary transformation. One approach is to decompose the unitary transformation into a product of basic quantum gates drawn from a universal gate set, where each gate in the set acts on at most 2 qubits simultaneously. Hence, the noise map acting on all n qubits associated with any two-qubit gate can be determined by applying the above protocol to other $n-2$ qubits while applying process tomography to the two qubits in the quantum gate. Another approach is to estimate the average error per gate for a sequence of m gates, such that the composition gives the identity operator. Such a sequence can be generated by making use of the cyclic property $U^m = 1$ of any gate in a universal gate set or by choosing a sequence of $m-1$ random gates followed by an m^{th} gate chosen such that the composition gives the identity transformation.

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Supporting Online Material

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Materials and Methods
SOM Text
Figs. S1 to S3
References

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Nuclei-Induced Frequency Focusing of Electron Spin Coherence

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The hyperfine interaction of an electron with the nuclei is considered as the primary obstacle to coherent control of the electron spin in semiconductor quantum dots. We show, however, that the nuclei in singly charged quantum dots act constructively by focusing the electron spin precession about a magnetic field into well-defined modes synchronized with a laser pulse protocol. In a dot with a synchronized electron, the light-stimulated fluctuations of the hyperfine nuclear field acting on the electron are suppressed. The information about electron spin precession is imprinted in the nuclei and thereby can be stored for tens of minutes in darkness. The frequency focusing drives an electron spin ensemble into dephasing-free subspaces with the potential to realize single frequency precession of the entire ensemble.

The possibility of encoding quantum information in the spins of quantum dot (QD) electrons has attracted considerable attention (*1*, *2*). The spatial confinement protects the spins against the primary relaxation mechanisms in bulk, all of which arise from coupling of spin and orbital momenta. However, the electron hyperfine interaction with the lattice nuclei is enhanced by confinement, leading to spin decoherence and dephasing (*3*–*10*) and thus posing severe difficulties for processing quantum information. General schemes for suppressing decoherence have been discussed already (*11*). Electron spin relaxation in QDs may be overcome by polarizing the nuclear spins (*12*, *13*), but the high degree of polarization required, close to 100% (*12*), has not been achieved yet (*14*–*16*).

We find that the hyperfine interaction, rather than being detrimental, can be used as a precision tool by demonstrating that it modifies the continuous mode spectrum of the electron spin precession in a QD ensemble into a few discrete modes. The information on this digital spectrum can be stored in the nuclear spin system for tens of minutes because of the long nuclear memory times (*17*, *18*).

In a QD ensemble, fast electron spin dephasing arises not only from nuclear field fluctuations but also from variations of the electron g factor, leading to different spin precession frequencies. The dephasing due to these unavoidable variations can be partly overcome by mode-locking (*19*), which synchronizes the precession of specific electron spin modes in the ensemble with the clocking rate of a periodic pulsed laser. Still, it leaves a substantial fraction of dephased electron spins, whose precession frequencies do not satisfy the mode locking conditions. We demonstrate that the nuclear spin polarization adjusts the electron spin precession frequency in each quantum dot such that the whole ensemble becomes locked on very few frequencies.

The experiments were done on an ensemble of self-assembled (In,Ga)As/GaAs QDs (*19*, *20*), each dot containing on average a single electron (*21*). The electron spin precession about a perpendicular magnetic field was studied by a pump-probe Faraday rotation (FR) technique with ps time resolution (*22*). Spin coherence is generated

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by circularly polarized pump pulses with wave vector parallel to the structure growth axis (z axis) and detected by rotation of the linear polarization of probe pulses. The excitation laser emits pulses with 1.5-ps duration at a rate of 75.6 MHz, equivalent to a pulse separation T_R = 13.2 ns (see sketch in Fig. 1A). The excitation is resonant with the ground state charged exciton consisting of two electrons with opposite spins and a hole.

The top trace in Fig. 1A shows a FR signal of the QD ensemble, created by a single pump pulse train. The signal at positive delays shows a fast decay on a ns time scale due to dephasing of the spin coherence by the ensemble spread of precession frequencies. The modulation arises from neutral exciton contributions (*20*). The signal at negative delays is due to constructive interference of electron spin precession modes fulfilling the phase synchronization conditions (PSC): $\omega = 2\pi K/T_R$, where K is an integer (*19*).

Much more flexible tailoring of the mode-locked distribution of spins is possible through a two pump pulse protocol (*23*). Each pump pulse was split into a doublet with a delay $T_D = 1.86\ \text{ns} \approx T_R/7$ between the two pulses (Fig. 1A). The corresponding FR signal is shown by the middle trace in Fig. 1A. Excitation by such a pump doublet leads to a sequence of FR signal bursts, which appear not only at the moments of pump pulse arrival but also periodically before and after the pump doublet with a period equal to T_D. These bursts arise from constructive interference of modes satisfying the two pulse protocol PSC of $\omega = 2\pi K/T_D$ (*23*).

The FR signal pattern created by the two pulse protocol is memorized over minutes. One would expect that blocking of the second pulse in a pump doublet would destroy the periodic FR burst pattern on the μs time scale of the electron spin coherence time, T_2, in these dots (*19*). Only the FR signal around the first pump should remain over the scanned range of pump-probe delays. Recording of the middle trace in Fig. 1A had the sample illuminated for ~20 min by the pump-doublet train. Immediately after this measurement, the second pump was blocked, and a FR measurement using only the single pump train was started (bottom trace in Fig. 1A) beginning from negative delays. Contrary to the expectations, the signal shows qualitatively all features of a pump doublet protocol. A strong FR signal ("burst 0") appears around the delays where the second pump was located. Further signals, denoted burst 1 and burst 2, also appear. The system therefore remembers for minutes its previous exposure to a two pump protocol. The decay of the burst amplitude with the increasing burst number is due to the increasing time at which the corresponding signal was recorded since switching off pump 2.

We have recorded FR traces in a short delay range around burst 0 for different times after closing the second pump. In these traces (Fig. 1B), we observe a strong FR signal even after 40 min. Because no phase shift between the FR traces occurs, we can record the decay kinetics at a fixed delay of 1.857 ns (corresponding to the maximum FR signal) versus time after switching off pump 2 (blue curve in Fig. 1C). The observed dynamics can be well described by a bi-exponential dependence on elapsed time t, $a_1\exp(-t/\tau_1) + a_2\exp(-t/\tau_2)$, as shown by the red line fit to the data, from which we get a memory time τ_1 of 1 min, while τ_2 is 10.4 min. The decay, however, critically depends on the light illumination conditions. When the system is held in darkness (both pumps and probe are blocked), no relaxation occurs at all on an hour time scale. This is exemplified by the red circles in Fig. 1C, which give the FR amplitude when switching on pump 1 as well as the probe after a dark period t.

We have also examined how fast a two pump pulse train creates the periodic burst pattern in the

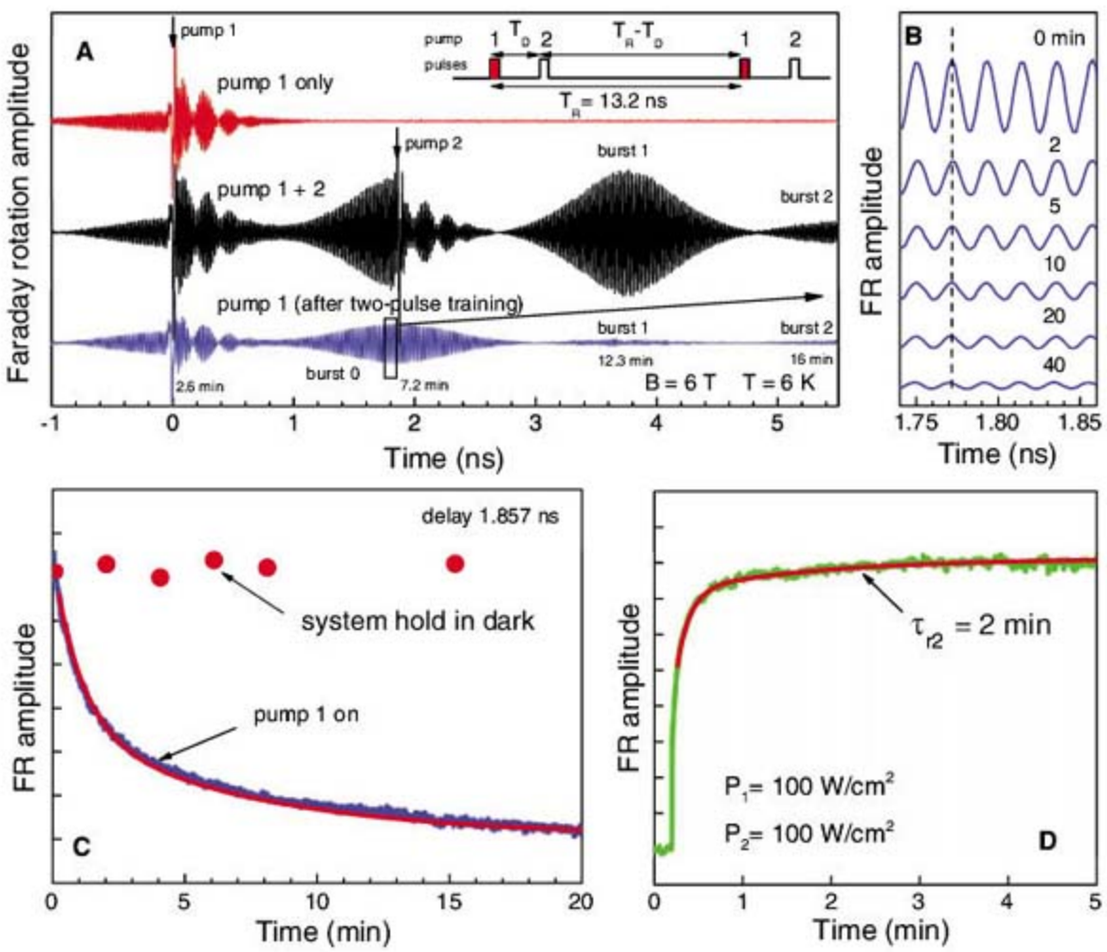

Fig. 1. (**A**) FR traces as function of delay time between probe pulse and first pump pulse measured on an ensemble of singly charged (In,Ga)As/GaAs quantum dots. The signals were scanned from negative to positive delays. Details of the optical excitation protocol are given in the sketch. The top trace was recorded for a single pump pulse train. For the middle trace we used a two pump pulse protocol with the second pump delayed by T_D = 1.86 ns relative to the first one. The lowest trace was taken for a single pump pulse. Recording started right after measurement of the middle trace. Some times at which the different FR signal bursts were measured are indicated. The pump and probe power densities were 50 and 10 W/cm^2, respectively. (**B**) FR signals measured over a small range of delay times around the burst 0 maximum [as indicated by the box in (A)] for different times after closing the second pump; at the same time, pump 1 and probe were always on. (**C**) Relaxation kinetics of the FR amplitude at a delay of 1.857 ns (maximum of burst 0) as a function of time after switching off pump 2. Beforehand, the system was treated for 20 min by the two pump pulse protocol. The blue curve was measured with pump 2 blocked at t = 0. The red line shows a bi-exponential time dependence fitted to the data. The red circles show the FR signal after keeping the system in darkness for different times and then addressing it by pump 1 and probe. (**D**) The kinetics of FR amplitude at the same delay of 1.857 ns when switching at t = 0 from the single to the two pump pulse protocol. The single pump pulse exposure before the switch lasted for 20 min. For each of the pumps the excitation density was 100 W/cm^2. The red line is a bi-exponential fit. For all panels B = 6 T and T = 6 K.

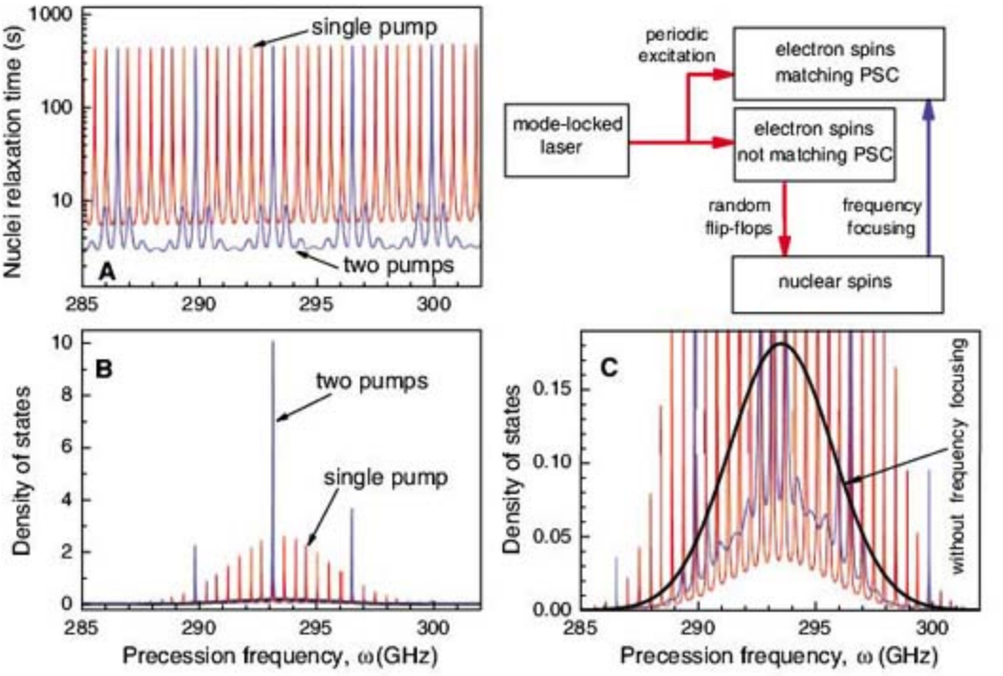

Fig. 2. Scheme of effects leading to the nuclei-induced frequency focusing of the electron spin precession modes. The periodic resonant excitation by a mode-locked circularly polarized laser synchronizes the precessions of electron spins whose frequencies satisfy the PSC. At the same time, the excitation leads to a nuclear rearrangement in those QDs, which do not satisfy the PSC, via optically stimulated electron-nuclear spin flip-flop processes. The rearrangement modifies the electron spin precession frequency such that it becomes frozen when the frequency reaches the PSC. (**A**) Average spin relaxation time of the As nuclei versus the electron spin precession frequency calculated for the single pump (red) and the two pump (blue) protocols. The spin relaxation time calculated in Eq. 11 in SOM text was derived by using (*30*, *31*). (**B**) Density of electron spin precession modes in an ensemble of singly charged QDs modified by the nuclei, calculated for the single pump (red) and the two pump (blue) protocols. The black line shows the density of modes before frequency focusing due to ensemble dispersion of electron g factor and nuclear polarization fluctuation. (**C**) A closeup of (B) for better visibility of the low density of states range. All calculations have been done for $B = 6$ T, $|g_e| = 0.555$, $\Delta g_e = 0.0037$, $\Delta\omega_{N,x} = 1$ GHz, $T_R = 13.2$ ns, $T_D = T_R/7$ ns, and $T_2 = 3$ μs.

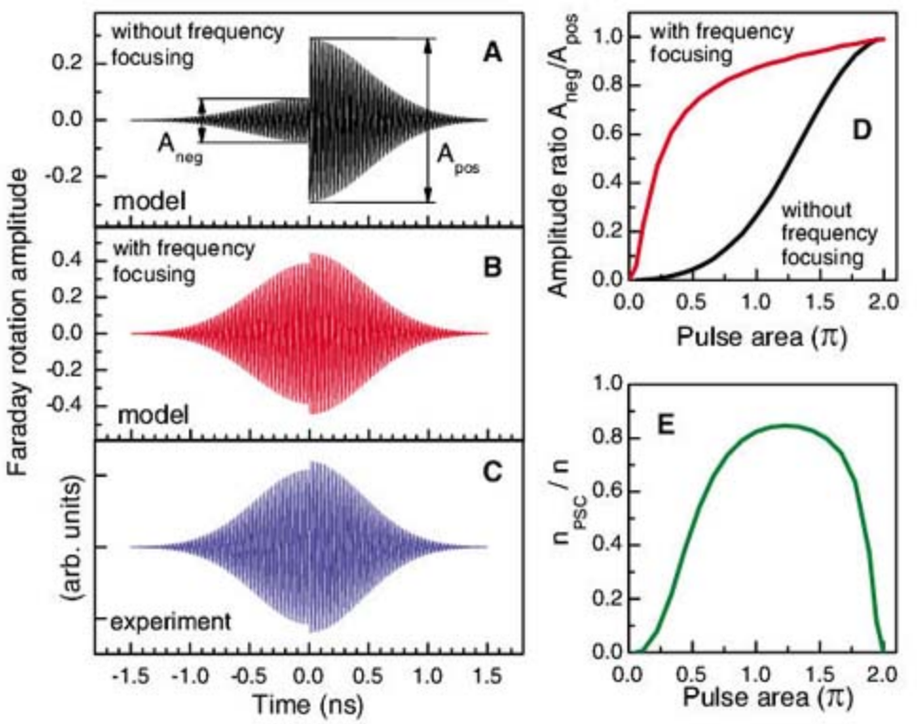

Fig. 3. (**A** to **C**) FR traces for an ensemble of singly charged QDs subject to a single pump pulse excitation protocol with pulse area $\Theta = \pi$ at $B = 6$ T. (A) FR traces calculated with the density of electron spin precession modes unchanged by the nuclei. The ratio of the FR amplitudes before, A_{neg}, and after, A_{pos}, the pump pulse shows that only 30% of the electrons are involved in the mode-locked spin precession, leading to a reduced FR signal at negative delays compared with that of positive delays. (B) FR traces calculated with the density of electron spin precession modes modified by the nuclei. The ratio of the FR amplitudes A_{neg}/A_{pos} shows that 90% of electrons are now involved in mode-locked precession. (C) Experimental trace of the FR signal obtained after extracting the contribution from neutral excitons, which leads to modulation of the FR signal after pump pulse arrival (Fig. 1). The experimental ratio A_{neg}/A_{pos} confirms that 90% of the electrons are involved in the mode-locked precession in our experiment. (**D**) Calculated ratio of the FR signal amplitudes, A_{neg}/A_{pos}, with (red) and without (black) including nuclear rearrangement as function of pump pulse area. (**E**) Dependence of the relative number of electrons, n_{psc}/n, in a QD ensemble involved in the mode-locked precession as function of pump pulse area. The same set of parameters was used as in Fig. 2.

FR signal. For that purpose, the sample was first illuminated only by pump 1, and then pump 2 was switched on. Both pumps had a power of 100 W/cm^2. The rise of the FR signal was measured at a FR maximum within burst 1 as function of time elapsed after switching on pump 2 (Fig. 1D). The slow component of this rise, τ_{r2}, is on a minutes time scale, and it shortens with excitation power.

The observed long memory of excitation protocol must be imprinted in the QD nuclei, for which long spin relaxation times in high magnetic fields up to hours or even days have been reported (*24*, *25*). The nuclei in a particular dot must have been aligned along the magnetic field, B, through the hyperfine interaction with the electron during exposure to the pump train. This alignment, in turn, changes the electron spin precession frequency, $\omega = \omega_e + \omega_{N,x}$, where $\omega_e = g_e\mu_B B/(\hbar)$, μ_B is the Bohr magneton, g_e is the electron g factor, and the nuclear contribution, $\omega_{N,x}$, is proportional to the nuclear polarization. The slow rise and decay dynamics of the FR signal in Fig. 1 indicate that the periodic optical pulse train stimulates the nuclei to increase the number of QDs for which the electron spin precession frequencies satisfy the PSC for a particular excitation protocol.

What is driving the projection of the nuclear spin polarization on the magnetic field to a value that allows an electron spin to satisfy the PSC?

The nuclear polarization is changed by electron-nuclear spin flip-flop processes resulting from Fermi-contact hyperfine interaction (*26*). Such processes, however, are suppressed in a strong magnetic field because of the energy mismatch between the electron and nuclear Zeeman splittings by about three orders of magnitude. Flip-flop transitions, which are assisted by pho-

nons compensating this mismatch, have a low probability because of the phonon bottleneck in QDs (*27*, *28*). This explains the robustness of the nuclear spin polarization in darkness to over an hour (Fig. 1C).

Consequently the resonant optical excitation of the singlet trion becomes the most efficient mechanism in the nuclear spin polarization dynamics. The excitation process rapidly turns "off" the hyperfine field of a resident electron acting on the nuclei, and the field is subsequently turned on again by the trion radiative decay. Thereby it allows a flip-flop process during the switching without energy conservation.

The nuclear spin-flip rate for this mechanism is proportional to the rate of optical excitation of the electron, $\Gamma_1(\omega)$. According to the selection rules, the probability of exciting the electron to a trion by σ^+ polarized light is proportional to $1/2 + S_z(\omega)$, where $S_z(\omega)$ is the component of the electron spin polarization along the light propagation direction taken at the moment of pump pulse arrival. Therefore, the excitation rate $\Gamma_1(\omega) \sim [1/2 + S_z(\omega)]/T_R$. For electrons satisfying the PSC (*19*): $S_z(\omega) \approx -1/2$, the excitation probability is very low because of Pauli blocking. Because of a very long decoherence time, T_2, in our QDs, the excitation rate for these electrons is reduced by two orders of magnitude to $1/T_2$ from $1/T_R + 1/T_2$ for the rest of electrons (in our experiments $T_2/T_R \approx 200$) [Supporting Online Material (SOM) text].

Because of $\Gamma_1(\omega)$, the nuclear relaxation rate has a strong and periodic dependence on ω, with the period determined by the PSC of the particular excitation protocol: $2\pi/T_R$ for the single pulse train and $2\pi/T_D$ for the double pulse train (Fig. 2A). The huge difference in the nuclear flip rate explains why $\omega_{N,x}$ in each QD tends to reach the value allowing the electron spin to fulfill the PSC. In QDs with the electron spin not matching the PSC, the nuclear contribution to ω changes randomly because of the light stimulated nuclear flip-flop processes on a seconds time scale. The typical range $\Delta\omega_{N,x}$ of this contribution to ω is limited by statistical fluctuation of the nuclear spin polarization. For the studied (In,Ga)As QDs, $\Delta\omega_{N,x}$ is on a GHz scale (SOM text) and comparable with the separation between the phase-synchronized modes $2\pi/T_R \sim 0.48$ GHz. As a result, the nuclear contribution occasionally drives an electron to a PSC mode, where its precession frequency is virtually frozen on a minutes time scale. This leads to the frequency focusing in each QD and to accumulation of the QDs, for which electron spins match the PSC.

The frequency focusing modifies the spin precession mode density in the QD ensemble (Fig. 2B and its closeup in C). Without focusing, the density of the electron spin precession modes is Gaussian with a width

$$\Delta\omega = \sqrt{[\Delta\omega_{N,x}]^2 + [\mu_B \Delta g_e B/(h)]^2}$$, where Δg_e

is the g factor dispersion. Frequency focusing modifies the original continuum density to a comb-like distribution. Eventually the whole QD ensemble participates in a coherent precession locked on only a few precession frequencies. This suggests that a laser protocol (defined by a pulse sequence, width, and rate) can be designed to focus the electron-spin precession frequencies in the QD ensemble to a single mode. To calculate the spin precession mode density in Fig. 2, we have applied a "box model" (*29*), in which the electron wave function has a finite amplitude $1/\sqrt{V}$ inside the QD volume, V, and is zero outside (SOM text).

The quantitative appearance of the spin precession mode density depends strongly on the excitation protocol. The complex evolution of the mode density caused by the switching between pumping protocols is described by Eq. 16 in (SOM text). Some of its features observed in the FR signal can be explained qualitatively. For example, the almost instantaneous FR signal rise when switching from the single to the two pump pulse protocol in Fig. 1D can be traced to the 1/7 fraction of QDs that, after exposure to the single pump pulse protocol, already fulfill the PSC for the two pump pulse protocol without any nuclear rearrangement (Fig. 2B). In the opposite case of switching from two to single pump pulse excitation, almost all QDs, which satisfy the PSC before the switch, continue to be mode-locked afterward (Fig. 2C). Changes of nuclear spin polarization are suppressed in these QDs, leading to a dynamics in the minutes time range (SOM text) and explaining the slow FR signal decrease in Fig. 1C.

The focusing of electrons into PSC modes is directly manifested by the FR signals in Fig. 1A, because it causes comparable FR amplitudes before and after the pump pulses. The calculations demonstrate that, without frequency focusing, the FR amplitude at negative delays, A_{neg}, does not exceed 30% of the positive delay signal amplitude, A_{pos} (Fig. 3A). The strong optical pump pulses in the experiment address all QDs, and their total contribution should make the FR signal much stronger after the pulse than before, when only the mode-locked electrons are relevant. However, the nuclear adjustment increases the negative delay signal to more than 90% (Fig. 3B). This is in agreement with the experimental data in Fig. 3C, which show only the electron contribution to the FR signal. The large value of A_{neg}/A_{pos} confirms that in our experiment almost all electrons in the optically excited QD ensemble become involved in the coherent spin precession. The calculations of the intensity dependence of the ratio A_{neg}/A_{pos} show that the nuclear focusing increases the ratio of electrons involved in the coherent spin precession to their total number, n_{pse}/n, almost to unity, even at low excitation intensity (Fig. 3, D and E).

We have shown that the nuclei in singly charged QDs exposed to a periodic pulsed excitation focus almost all the electrons in the ensemble into a coherent electron spin precession. The exciting laser acts as a metronome and establishes a robust macroscopic quantum bit, which exists in dephasing free subspaces. This may open promising perspectives on the use of an ensemble of charged QDs with the single electron coherence time T_2.

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Supporting Online Material

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Late Archean Biospheric Oxygenation and Atmospheric Evolution

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High-resolution geochemical analyses of organic-rich shale and carbonate through the 2500 million-year-old Mount McRae Shale in the Hamersley Basin of northwestern Australia record changes in both the oxidation state of the surface ocean and the atmospheric composition. The Mount McRae record of sulfur isotopes captures the widespread and possibly permanent activation of the oxidative sulfur cycle for perhaps the first time in Earth's history. The correlation of the time-series sulfur isotope signals in northwestern Australia with equivalent strata from South Africa suggests that changes in the exogenic sulfur cycle recorded in marine sediments were global in scope and were linked to atmospheric evolution. The data suggest that oxygenation of the surface ocean preceded pervasive and persistent atmospheric oxygenation by 50 million years or more.

The history of Earth-surface oxygenation is written in the geological record of redox-sensitive elements preserved in ancient sediments. The discovery of large non–mass-dependent (NMD) S isotope anomalies in Archean and the earliest Paleoproterozoic sediments are believed to record changes in atmospheric O_2 levels, as these result from photochemical reactions in a low O_2 atmosphere (*1–4*). To document temporal changes in the magnitude of these isotope excursions, we focused on high stratigraphic resolution analyses of organic-rich shale and carbonate from a recently drilled scientific core (*5*) through the ~2500 million-year-old Mount McRae Shale of northwestern Australia. Previous studies of the Mount McRae Shale identified abundant 2-α methyl hopanoids (*6*), produced by cyanobacteria that most likely generated O_2, as well as eukaryotic sterols (*7*), which are biomolecules that require O_2 for their synthesis (*8*). We investigated the time-series history of elemental and isotope variations through the succession and interpreted the upper half of the formation as capturing the oxygenation of the terminal Archean surface ocean and biosphere, a result further supported by a companion trace-metals study (*9*).

In the present study, a modified online combustion method (*5*, *10*) for rapid analysis of whole-rock S and a high-precision fluorination technique for analysis of chemically extracted sulfide S were applied to samples from the core. We used unprecedented, high-resolution records ($\delta^{34}S$, $\Delta^{33}S$, and $\Delta^{36}S$) in concert with stratigraphic variations in elemental abundances [weight percent (wt %) C and S] and ^{13}C compositions of carbonate and organic matter to address the cause(s) of fluctuation in NMD effects preserved in these ancient sediments. These results were compared to a previous study of the Mount McRae Shale (*11*) and to new S isotope data from the stratigraphically equivalent Gamohaan and Kuruman Iron formations in South Africa (*12–14*) to evaluate the spatial extent of the interpreted events.

The Mount McRae Shale core intersects laminated and well-preserved sediments that accumulated in a marine environment below the wave base. A regional sequence analysis (*15*) indicates the presence of two depositional cycles; each sequence starts in carbonate or siliciclastic turbidite or breccia and deepens upwards to either pelagic shale or banded iron-formation (Fig. 1). The succession has experienced only mild regional metamorphism (prehnite-pumpellyite facies to <300°C) and minimal deformation (gentle folding to dips <5°) (*16*). Radiometric age constraints place the Mount McRae Shale very near the Archean/Proterozoic boundary (~2500 million years old) (*9*) and just before the disappearance of large NMD effects that are inferred to mark the rise in atmospheric O_2 (*1–3*, *17*).

Geochemical data from the Mount McRae Shale (Fig. 1) suggest a tight coupling between environmental and biological signals, with a substantial transition recorded at ~153 m in the core. Acid leaching of extractable iron from Mount McRae samples indicates that siderite dominates in the lower half of the formation, which is consistent with the absence of O_2 in deeper depositional environments. On the other hand, calcite is a primary carbonate phase in the upper Mount McRae Shale, indicating the general absence of soluble iron in the shallow water column at this time. Carbonate and total organic C $\delta^{13}C$ values increase progressively up the core. Total organic C and total S values are high throughout the Mount McRae Shale but are notably enriched above the mineralogic transition in the interval between 135 and 153 m, where up to 16 wt % C and S are observed. In the interval between 130 and 135 m, visual evidence of pyrite nodules, laminations, and graded beds suggests some degree of sulfide remobilization, which may help to explain the sharp drop in total S abundance in the homogeneous-shale host rock.

The high-resolution S isotope record reveals considerable stratigraphic variation in $\delta^{34}S$ and $\Delta^{33}S$ (*18*), including substantial bed-to-bed oscillations. In evaluating the time-series S isotope data, the Mount McRae Shale can be divided (*19*) into a lower unit (>153 m), where $\delta^{34}S$ and $\Delta^{33}S$ show positive correlation, and an upper unit (<153 m), where $\delta^{34}S$ values become increasingly negative. Of particular interest is the interval above 130 m, where positive $\Delta^{33}S$ values are coupled with negative $\delta^{34}S$ values; this S isotope relation may record an important environmental and biological event near the Archean/Proterozoic boundary.

The lower half of the Mount McRae Shale from the Archean Biosphere Drilling Project (ABDP)–9 core is interpreted to have accumulated in a deep, anoxic environment insofar as sediments are dominated by sideritic shale and banded iron-formation (*13*, *14*). The positive correlation between $\delta^{34}S$ and $\Delta^{33}S$ in the lower Mount McRae Shale has been interpreted as either a primary atmospheric array (*11*) or mixing between atmospherically derived NMD S with mass-dependent terrestrial inputs. This mixing may well explain the long-term and bed-to-bed variability in S isotope compositions (Figs. 1 and 2B). It is difficult to independently assess the quantitative contribution of terrestrial inputs [with $\delta^{34}S$ and $\Delta^{33}S \sim 0$ per mil (‰)] relative to NMD inputs. However, nonzero values of $\Delta^{33}S$ (either positive or negative) must ultimately be linked to fluxes of sulfate and elemental S from the atmosphere. We interpret the dominance of positive $\Delta^{33}S$ through this stratigraphic interval as indicating the preferential incorporation of reduced NMD S (atmospheric elemental S) into marine sediments, probably facilitated by microbial elemental S reduction. This microbial process is capable of transferring the $\Delta^{33}S$ to pyrite, while imparting little to no additional isotopic fractionation in $\delta^{34}S$. Ono *et al.* (*11*) previously explained variations in NMD signatures within the Mount McRae strata by physical and biological mixing of these atmospheric sources. The isotopic similarity (in $\delta^{34}S$ and $\Delta^{33}S$) between their core and ours, presently 300 km apart, points to a basin-scale phenomenon linked through atmospheric inputs (*20*). However, rapid bed-to-bed (or even within bed) variability and small differences in the magnitude of the positive $\Delta^{33}S$ excursion probably reflect local controls related to variable mixing of S from distinct surface reservoirs, including the deep and shallow ocean as well as terrestrial environments.

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As noted above, the upper half of the Mount McRae Shale, which is dominated by turbidites of carbonate and shale that accumulated below the storm wave base, is characterized by sulfides with negative $\delta^{34}S$ values coupled with positive $\Delta^{33}S$ values (Figs. 1 and 2A). The $\delta^{34}S$ and $\Delta^{33}S$ values of these sulfides imply microbial sulfate reduction with larger isotopic fractionations, which may reflect sulfate reduction in the water column (*21*), possibly coupled with rising sulfate concentrations (*22*). This interpretation is consistent with the high organic C contents in sediments above 153 m in the core, which are plausibly linked to high rates of primary productivity that released oxidants into the shallow marine environment. On the other hand, the positive $\Delta^{33}S$ values reflect incorporation of reduced photolytic S. To account for these two features, we propose that the S isotope signatures in the upper Mount McRae Shale reflect the establishment of a widespread and possibly permanent oxidative S cycle, perhaps for the first time in Earth's history, in a water column that was stratified with respect to oxygen (*23*).

In the late Archean oceans, O_2 would accumulate in highly productive regions along continental margins and perhaps to a lesser degree in distal settings, where nutrient levels were high enough to stimulate oxygenic photosynthesis. Possible explanations to account for the isotopic observations above 153 m include elemental S reducers capable of producing large ^{34}S depletions (an unlikely scenario given the small redox change associated with this metabolic pathway) or the activation of microbial disproportionation reactions (*24*). Because the former are currently unknown and the latter are not clearly evident until the mid-Proterozoic (*25*), we suggest an alternative solution related to increases in O_2 initiated during the productivity event recorded in the core above 153 m. Inorganic S oxidation generally requires high levels of dissolved O_2, whereas microbial S oxidation, which is thought to be ancient in origin, would proceed at lower (or absent) O_2 concentrations but still would require an electron acceptor to drive phototrophic oxidation. In either case, the magnitude of isotopic fractionation associated with oxidation is small (*26*) and unlikely to account for the negative $\delta^{34}S$ values of sulfides in the upper Mount McRae sediments. Thus, we propose that the sulfate formed through oxidation (with positive $\delta^{34}S$ and $\Delta^{33}S$) was re-reduced by microbial sulfate reduction to form sulfides depleted in $\delta^{34}S$ but retaining positive NMD $\Delta^{33}S$ values (Figs. 1 and 2A).

The organic C and S spike between 153 and 135 m corresponds to an interval where both $\delta^{34}S$ and $\Delta^{33}S$ values are typically negative (*19*). Although broadly binned with the upper Mount McRae Shale interval, these sediments provide important environmental constraints on a source of S (with a negative $\Delta^{33}S$ composition) and the mechanism for its sink into sediments. Low Archean atmospheric O_2 levels would generally limit oxidative weathering, the principal source of sulfate to the modern oceans. With rising atmospheric O_2 levels, however, some metals and associated S from terrestrial sources may have been released to the shallow marine environment (*9*), but contributions from juvenile S ($\Delta^{33}S = 0$) or preexisting sedimentary sources ($\Delta^{33}S > 0$) cannot account for the negative $\Delta^{33}S$ value of the S from this interval. Thus, a major source of sulfate to the Archean ocean at this time would have been atmospheric in origin and would have carried a negative $\Delta^{33}S$ signature

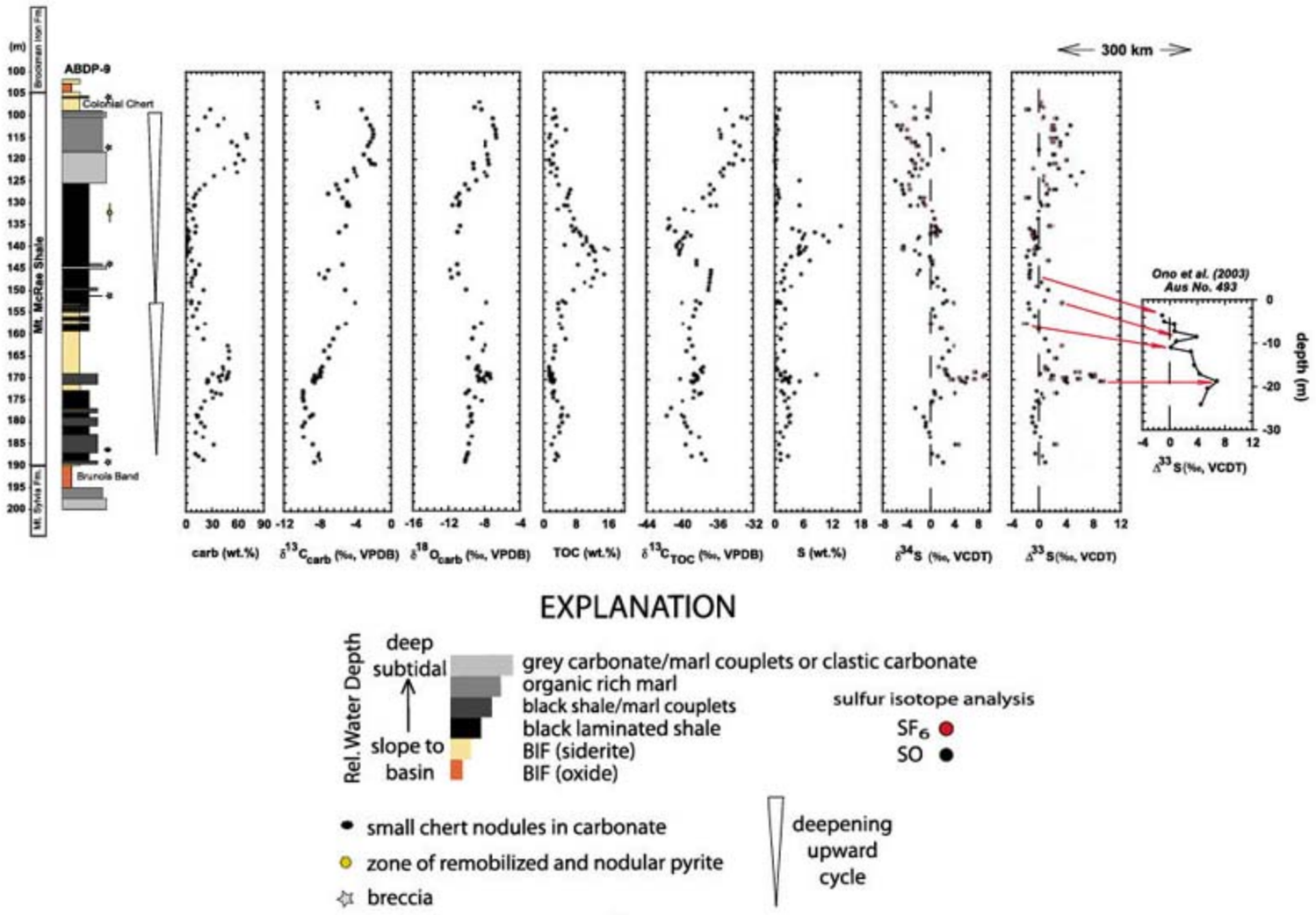

Fig. 1. Lithologic and time-series elemental (C and S) and isotopic ($\delta^{13}C$, $\delta^{18}O$, $\delta^{34}S$, and $\Delta^{33}S$) trends in the ~2500 million-year-old Mount McRae Shale. Sequence subdivisions are based on (*15*). Trends in $\Delta^{33}S$ in the lower Mount McRae Shale are correlated with equivalents in a separate core drilled some 300 km away from the core in this study (*11*). VPDB, Vienna Pee Dee belemnite; TOC, total organic C; VCDT, Vienna Canyon Diablo Triolite.

(*1*, *4*). In keeping with previous arguments for Archean seawater sulfate (*27*), we interpret deep- and open-ocean seawater sulfate as having a negative $\Delta^{33}S$ composition and acting as the major source of S in the pyritic interval above 153 m. Sulfate in the anoxic deep ocean was nonetheless likely to have been low (potentially <200 μM) (*22*) and possibly even lower on the continental shelves. However, we suggest that enhanced microbial sulfate reduction, stimulated by high rates of organic C burial in the presence of abundant reactive iron, would serve as an effective long-term sulfate sink and conceivably result in the concentration of open-ocean S (with negative $\Delta^{33}S$) into the sediments (*28*).

Further insight into the Archean S cycle, specifically atmospheric evolution, is gained through the evaluation of the $\Delta^{36}S/\Delta^{33}S$ relation. Whereas mass-dependent processes fractionate ^{33}S and ^{36}S in systematic ways ($\Delta^{36}S/\Delta^{33}S \sim -7$) (*29*, *30*), NMD photochemical experiments (*2*, *31*) suggest a wavelength dependence to the $\Delta^{36}S/\Delta^{33}S$ relation, and with a few exceptions, observations from the Archean record generally follow $\Delta^{36}S/\Delta^{33}S \sim -1$. This value is broadly consistent with measurements of sulfides from a wide range of Archean sediments (*1*, *32*). Additionally, the $\Delta^{36}S/\Delta^{33}S$ relation may characterize NMD contributions to surface environments even when the absolute magnitude of $\Delta^{33}S$ is small (*33*, *34*). The high-resolution ^{36}S analysis of the Mount McRae Shale reveals measurable differences for $\Delta^{36}S/\Delta^{33}S$ within the succession (Fig. 2, C and D), further supporting the stratigraphic distinctions outlined above. The resolvable difference between the $\Delta^{36}S/\Delta^{33}S$ relation in the upper and lower Mount McRae Shale indicates a change in atmospheric composition, because according to current knowledge, such shifts can only be caused by changing photochemical reactions involving S-bearing gases (*35*).

If the change in atmospheric composition suggested above is real, we expect the signal to be widespread in nature. To test this prediction, we have undertaken S isotope analyses of samples from the broadly equivalent Transvaal Basin in South Africa. The studied South African core intersects the Gamohaan and Kuruman Iron Formations (*5*, *12*, *13*, *36*), which record similar lithologic transitions to those observed in northwestern Australia. Although it is possible that these two successions (now over 8000 km apart) accumulated along the margins of a contiguous ocean basin, palinspastic reconstruction (*37*) of the two subbasins on the basis of existing outcrop area suggests that the core locations were at least 1000 km apart when the sediments accumulated.

The similarity in S isotope records between the South African and Australian sediments is pronounced (Fig. 2). The correlation between these widely separated basins strongly supports the spatially pervasive character of $\Delta^{33}S$ (and $\Delta^{36}S$) production, implying a degree of lateral atmospheric homogeneity. The $\Delta^{36}S/\Delta^{33}S$ of the lower portion of the South African core matches that of the lower Mount McRae Shale, whereas the $\Delta^{36}S/\Delta^{33}S$ from the upper portion is quite similar to that of the upper Mount McRae sediments. The consistency of the $\delta^{34}S$ versus $\Delta^{33}S$ and $\Delta^{33}S$ versus $\Delta^{36}S$ relations between the Australian and South African cores indicates that the S isotope variations reflect widespread and probably global variations in the Archean S cycle. The origin of the profound $\delta^{34}S$ and $\Delta^{33}S$ anomaly at ~170 m in the Mount McRae core and its equivalent in South Africa is unknown, but it is probably related to a pulsed flux of atmospheric inputs to surface environments that was captured over long distances in similar depositional settings. Whereas the transition captured at ~153 m might reflect changes in the atmospheric O_2 budget, it is also possible that changes in the abundance of other atmospheric species (CO_2 and CH_4) may be responsible for differences in the $\Delta^{36}S/\Delta^{33}S$ relations. However, the independent trace-metal evidence (*9*) and lower stability of methane under oxidizing conditions point to an increasingly important role for O_2 in surface environments.

We interpret our data from Western Australia and South Africa to suggest a progressive oxygenation of the Archean biosphere. This conclusion is in accord with the trace-metal data (*9*), which similarly suggest the onset of oxidative processes. Combined, these time-series records of mineralogic, elemental, and S isotopic change provide clues to coupled changes in the redox state of the shallow ocean (largely before the atmosphere became oxygenated) in relation to biological innovation before the Archean/Proterozoic boundary, including the oldest evidence for an active and globally distributed oxidative S cycle.

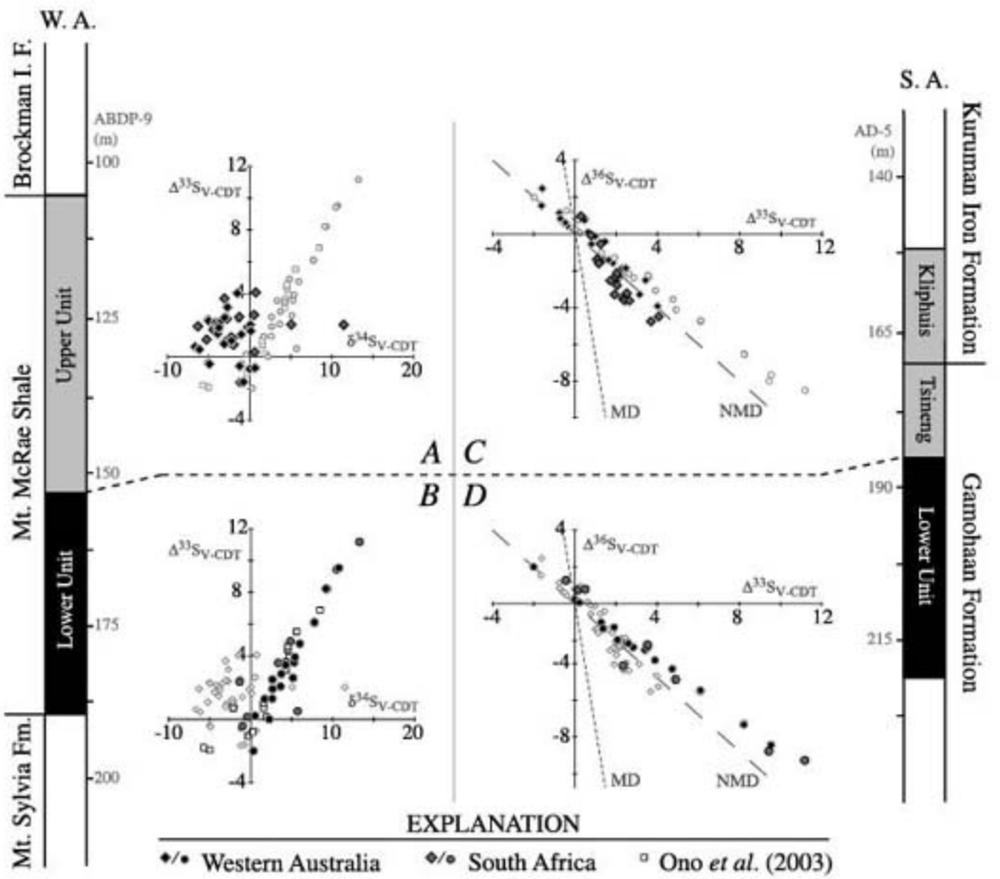

Fig. 2. Triple isotope plots [$\delta^{34}S$ versus $\Delta^{33}S$ in **(A)** and **(B)** and $\Delta^{33}S$ versus $\Delta^{36}S$ in **(C)** and **(D)**] for the Mount McRae Shale in Western Australia (W. A.) and the equivalent Gamohaan and Kuruman formations in South Africa (S. A.). Data from both cores are divided into upper [(A) and (C)] and lower [(B) and (D)] intervals. All data outside the target stratigraphic interval is shown in light gray for comparison. The anomalous S isotope compositions recorded in (A) are interpreted as reflecting oxidizing conditions. Mass-dependent fractionations of ^{33}S and ^{36}S resulted in an array with a slope of ~6.85 (*30*, *32*) [labeled as MD in (C) and (D)], whereas data from this study fit the general Archean slope of ~−1 (*1*). The $\Delta^{33}S$ versus $\Delta^{36}S$ relation between the correlated upper and lower intervals is statistically different, pointing to the evolution of atmospheric composition in the late Archean Eon. I. F., iron formation.

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18. All bulk samples were analyzed by the sulfur monoxide method in triplicate, and the reported values are averages of these measurements. Uncertainties are better than 0.3‰ for both $\delta^{34}S$ and $\Delta^{33}S$ values, which is comparable with uncertainties based on multiple standard measurements during each analytical session. For SF_6 analyses, uncertainties are 0.14, 0.008, and 0.20‰ for $\delta^{34}S$, $\Delta^{33}S$, and $\Delta^{36}S$, respectively.
19. Monte Carlo resampling of data suggests that the two intervals carry a unique isotopic mean. In the lower half, we calculated means of $\delta^{34}S = 3.04$ (±0.50) and $\Delta^{33}S = 1.98$ (±0.44). In the upper half, including the organic and pyrite-rich horizon, the data indicate means of $\delta^{34}S = -1.41$ (±0.34) and $\Delta^{33}S = 1.10$ (±0.29). Considered alone, data from the pyritic interval between 153 and 135 m indicate means of $\delta^{34}S = -0.80$ (±0.47) and $\Delta^{33}S = -0.54$ (±0.17).
20. Atmospheric photochemistry is presently the only known mechanism that can account for the nonzero $\Delta^{33}S$ data and their relationship to $\Delta^{36}S$ values in the Archean record (*1–4*, *17*). The principal source of S in the Archean atmosphere was volcanic (although biogenic sources may have also existed). Gas-phase photochemistry involving sulfur dioxide or sulfur monoxide has been shown in closed-cell photochemical experiments (*2*) to result in NMD sulfate (SO_4^{2-}; with negative, and in some cases positive, $\Delta^{33}S$ values) and elemental S (S_8, with positive $\Delta^{33}S$ values). These reactions are sensitive to the wavelength of available ultraviolet radiation, and this parameter depends on, among other things, atmospheric O_2 concentrations. The transfer pathways of S from the atmosphere to Earth's surface also depend on O_2 concentration. An atmospheric model (*4*) constrains an upper limit of $<10^{-5}$ of present atmospheric levels of O_2 for the transfer of nonzero $\Delta^{33}S$ (and $\Delta^{36}S$) containing SO_4^{2-} and S_8 to Earth's surface; at a higher partial pressure of O_2, the two S reservoirs homogenize in the atmosphere, and the photochemical signal is not preserved.
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SOM Text
Figs. S1 to S4
Tables S1 and S2
References

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A Whiff of Oxygen Before the Great Oxidation Event?

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High-resolution chemostratigraphy reveals an episode of enrichment of the redox-sensitive transition metals molybdenum and rhenium in the late Archean Mount McRae Shale in Western Australia. Correlations with organic carbon indicate that these metals were derived from contemporaneous seawater. Rhenium/osmium geochronology demonstrates that the enrichment is a primary sedimentary feature dating to 2501 ± 8 million years ago (Ma). Molybdenum and rhenium were probably supplied to Archean oceans by oxidative weathering of crustal sulfide minerals. These findings point to the presence of small amounts of O_2 in the environment more than 50 million years before the start of the Great Oxidation Event.

Many lines of evidence point to a rapid rise in the partial pressure of atmospheric O_2 (P_{O_2}) from $<10^{-5}$ times the present atmospheric level (PAL) between 2.45 and 2.22 billion years ago (Ga) (*1*, *2*), a transition often referred to as the Great Oxidation Event (GOE). The GOE could have been an immediate consequence of the evolution of oxygenic photosynthesis (*3*). Alternatively, O_2 biogenesis may be ancient (*4*). If so, the GOE was a consequence of an abiotic shift in the balance of oxidants and reductants at Earth's surface (*5–8*). This debate can be addressed by looking for evidence of localized or short-lived concentrations of O_2 before 2.45 Ga.

The abundances of some transition elements in sedimentary rocks are sensitive to the availability of O_2 (*9*). In particular, in the modern oxygenated environment, molybdenum (Mo) exists in rivers and oceans primarily as the unreactive molybdate ion (MoO_4^{2-}). Oxidative weathering of Mo-bearing sulfide minerals in crustal rocks leads to the accumulation of Mo in the oceans, where it is the most abundant transition element (at a concentration of ~105 nM) (*10*, *11*). The abundance of Mo in the oceans is reflected in

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pyritic marine sediments deposited under oxygen-deficient conditions, where Mo is removed from solution in association with organic carbon (*12*, *13*), probably after reacting with H_2S to form oxythiomolybdates ($MoO_{4-x}S_x^{2-}$) (*14*). In such sediments deposited today and through much of the Phanerozoic, Mo contents are typically >100 ppm versus ~1 ppm in average crust (*10*, *12*, *13*, *15*, *16*).

By comparison, on an anoxic Earth, Mo would be largely retained in unoxidized crustal sulfide minerals during weathering. Therefore, Mo concentrations in the oceans would be low, and organic-rich sediments would show little authigenic Mo enrichment as compared to modern equivalents. Similar logic applies to sulfur (S). In fact, studies of Mo and S concentrations and stable isotopes in black shales reveal systematic shifts in ocean budgets from the Archean through the Phanerozoic that are broadly consistent with the GOE and with another rise in P_{O_2} later in the Proterozoic (*2*, *17*–*19*) (table S1). Rhenium (Re) and uranium (U) are also promising indicators because their aqueous geochemistry is similar to that of Mo.

Here we report Mo, Re, U, and S measurements, as well as other geochemical data obtained at high stratigraphic resolution in the Mount McRae Shale, deposited ~2.5 Ga in the Hamersley Basin, Western Australia (*20*, *21*). Approximately 100 samples were analyzed from a freshly recovered continuous drill core obtained for this study (*22*) (Fig. 1, fig. S1, and table S2). These samples were also analyzed for S isotope variations as part of a companion study (*23*).

The core intersected two intervals containing pervasive pyritic carbonaceous shale, which we refer to as S1 (from 125.5 to 153.3 m) and S2 (from 173.0 to 189.65 m). Shales in both intervals contain several weight % (wt %) S and typically >3% total organic carbon (TOC), which is consistent with anoxic (and potentially sulfidic) bottom waters and the presence of H_2S in pore waters during these depositional intervals.

The most prominent feature of the data is the excursion in Mo content within S1 (Fig. 1). Mo concentrations below this layer are typically <5 parts per million (ppm), which is near the crustal value and is typical of Archean carbonaceous shales. Concentrations increase gradually up the section from the base of S1 to a peak value of ~40 ppm at 143 m and then decrease to <10 ppm by ~125 m. These variations and the Mo peak at ~143 m are more pronounced when plotted as aluminum (Al)–normalized enrichment factors (*24*). Viewed this way, Mo content increases up the section by ~50 times before falling sharply over an interval of ~2 m. The Mo enrichment correlates with enrichments in TOC and Re and broadly coincides with variations in carbonate and S contents. However, U contents vary little through the section.

The coherent behavior of Mo, Re, and U makes it possible to use Re/Os geochronometry to verify that metal abundances were unaffected by remobilization. Postdepositional addition or loss of Re (or Os) would result in significant isochron scatter. We find that samples taken from 128 to 149 m define an isochron with mean square weighted deviation = 1.1 (*22*) (Fig. 2 and table S3) and an age of 2501.1 ± 8.2 million years, which is consistent with previous ages for the Mount McRae shale (*20*, *21*). The element enrichments are therefore primary sedimentary features (as is the lack of associated U variation) deposited at the boundary of the Archean and Proterozoic eons, at least 50 million years before the beginning of the GOE.

The Mo excursion cannot be explained by variable carbonate dilution, as documented by extreme enrichment factors (Fig. 1). Instead, the correlations of Mo with TOC are strong evidence of authigenic enrichment (Fig. 3). Such trends are common in sediments from modern anoxic

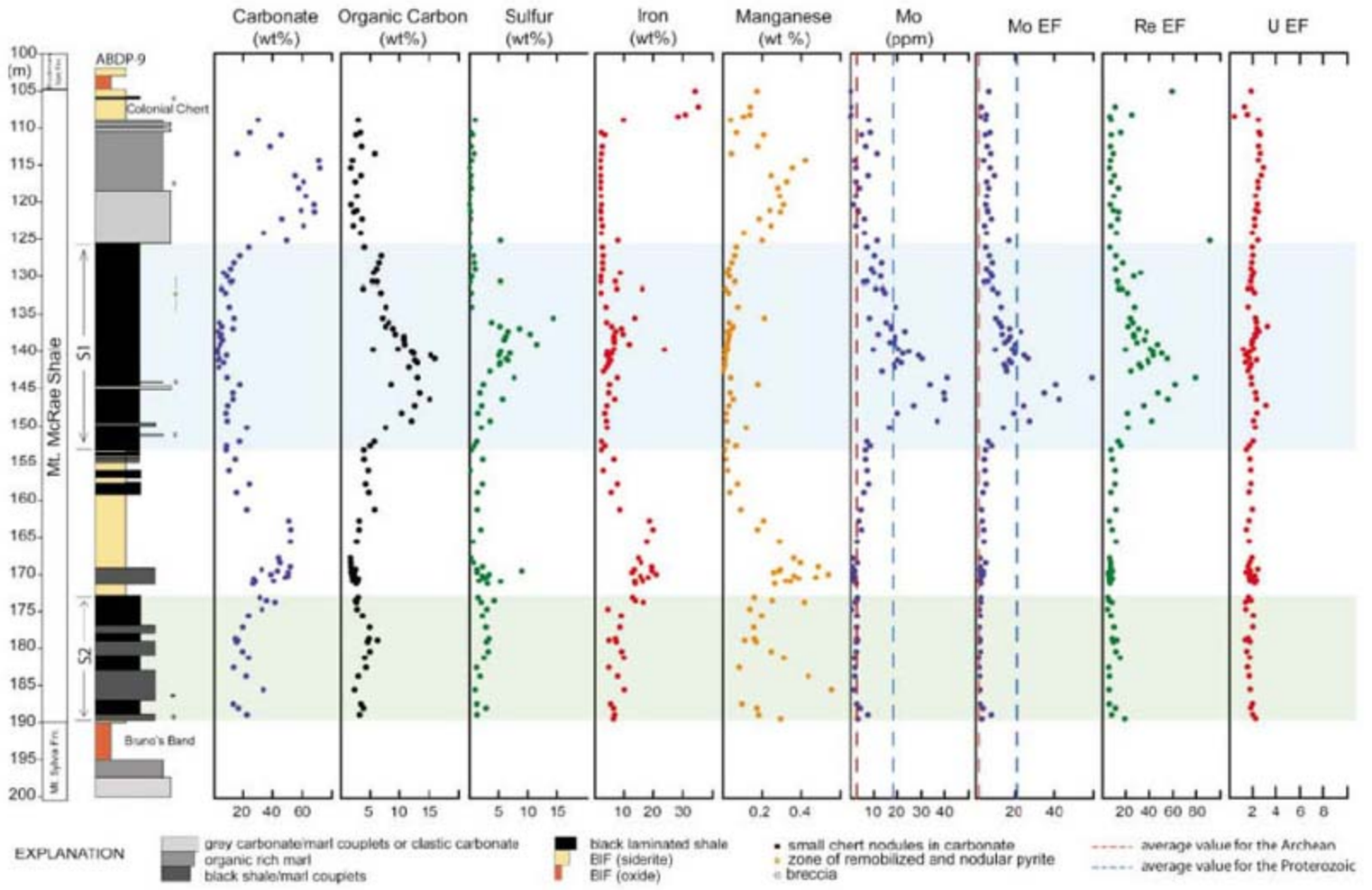

Fig. 1. Stratigraphy and geochemistry of the Mount McRae Shale, including percent of carbonate, TOC, S, Fe, Mn, Mo, Re, and U and EFs (*24*) for Mo, Re, and U (*23*). The intervals S1 and S2 span 125.5 to 153.3 m and 173.0 to 189.7 m, respectively. For comparison, dashed lines denote mean Mo concentrations and EFs in Archean and Proterozoic pyritic black shales, as indicated in the legend at bottom (*18*, *22*) (tables S1 and S2).

basins where the concentration of H_2S exceeds ~10 μM. In such sediments, Mo/TOC scales with Mo concentrations in deep waters (*12*). We recognize two trends within S1, corresponding to the zone of increasing Mo enrichment (~143 to 153 m) and the overlying zone in which Mo falls but remains elevated above average crustal values (~125 to 143 m). Mo/TOC slopes in these zones are ~3.4 ± 0.5 (±1σ) ppm Mo/wt % TOC and ~1.8 ± 0.2 (±1σ) ppm Mo/wt % TOC, respectively (*25*). By comparison, Mo/TOC is 4.5 to 25 ppm Mo/wt % TOC in pyritic sediments from modern anoxic basins (*12*) and averages ~26 ppm Mo/wt % TOC in Phanerozoic pyritic black shales (*18*) (table S1). Hence, small but substantial concentrations of dissolved Mo were present during S1 deposition. Similar reasoning can be applied to Re (fig. S2A).

These observations are not easily explained by hydrothermal inputs to the oceans. Enhanced hydrothermal input should result, first and foremost, in enrichments of iron (Fe) and manganese (Mn), yet the S1 unit is depleted in these elements relative to S2. In any event, high-temperature mid-ocean ridge–type systems should be sinks, not sources, for Mo and Re because of the low solubilities of Mo and Re sulfides. A small amount of Mo enters seawater today as result of low-temperature hydrothermal seafloor weathering (*13*), but this Mo is probably derived from modern Mo-rich seafloor sediments.

Instead, these observations can be straightforwardly interpreted as evidence of oxidative weathering during S1 deposition. We hypothesize that O_2 in the shallow oceans and possibly in the atmosphere enhanced the rate of dissolution of submarine and subaerial sulfide minerals, such as molybdenite (MoS_2), that are important for the budgets of Mo and Re in igneous and metamorphic crustal rocks. Mo and Re released in this way would ultimately have produced authigenic enrichments in ocean sediments.

Sulfide minerals weather rapidly in the presence of O_2, so P_{O_2} need not have been high. For example, even if P_{O_2} is only ~10^{-5} PAL, a pyrite crystal of 100 μm^3 volume will dissolve completely in <~20,000 years (*26*, *27*). This is a short time compared to the likely duration of S1 (*28*). Consistent with such low P_{O_2}, Mo/TOC values in S1 do not exceed those of sediments accumulating in the modern Black Sea, which implies that the concentration of Mo in contemporaneous seawater was of similar magnitude as that in the deep waters of the Black Sea, or <1% that of fully oxygenated modern oceans.

The same process could have contributed to the excursion in S content and $\delta^{34}S$ in S1 (*23*). The long-term $\delta^{34}S$ record of sedimentary sulfides exhibits a negative shift between 2.4 and 2.3 Ga that is thought to indicate an increase in ocean sulfate concentrations. This increase is ascribed to an increased rate of oxidative weathering of pyrites in crustal rocks during and after the GOE (*2*). The negative shift in sedimentary $\delta^{34}S$ beginning at ~153 m in the Mount McRae Shale may record the effects of less extreme oxygenation at 2.5 Ga.

Our hypothesis of mild oxygenation is supported by the absence of U enrichment coincident with Mo and Re enrichments (Fig. 1) and the lack of correlation between U and TOC in S1 (fig. S2B), observations indicating that dissolved U concentrations were very low. U in the crust is primarily hosted by feldspars, zircon, apatite, and sphene, but not sulfides. Therefore the rate of release of U from rocks is only weakly affected by oxygenation, unlike that of Mo and Re; experimental studies suggest that the rate of pyrite oxidation exceeds that of feldspar minerals when $P_{O_2} > 10^{-6}$ PAL (*29*, *30*). U may also be less mobile than Mo and Re when O_2 is low (*31*). Hence, enhancements of Mo and Re influx without U enhancement are expected in the presence of small amounts of O_2.

Our interpretation is also consistent with the extremely nonradiogenic initial $^{187}Os/^{188}Os$ in the Mount McRae Shale (Fig. 2). Such low values, also seen in shales ~200 million years younger (*32*), indicate that the ocean Os budget was dominated by hydrothermal sources rather than by radiogenic Os derived from the weathering of high-Re/Os crustal rocks. As with U, oxidative weathering of sulfide minerals in igneous or metamorphic rocks might have had little effect on the balance between hydrothermal and crustal sources of Os to the oceans, because the Os content of crustal sulfide minerals, particularly molybdenite, can be low.

The low levels of O_2 that can account for our data are similar to the upper limit of 10^{-5} PAL for typical Archean P_{O_2} derived from the observation of nonzero $\Delta^{33}S$ in Archean sediments (*33*, *34*), possibly explaining the juxtaposition of Mo and Re enrichments with the small nonzero $\Delta^{33}S$ signals seen throughout S1 (*23*). Alternatively, P_{O_2} above this threshold could have been present ephemerally within geographically restricted areas such as biologically productive regions of the oceans.

In contrast to the observations in S1, Mo concentrations and enrichment factors are very low below ~153 m, including in the organic carbon–rich and pyritic S2, where Mo is essentially invariant with TOC [Mo/TOC = 0.15 ±

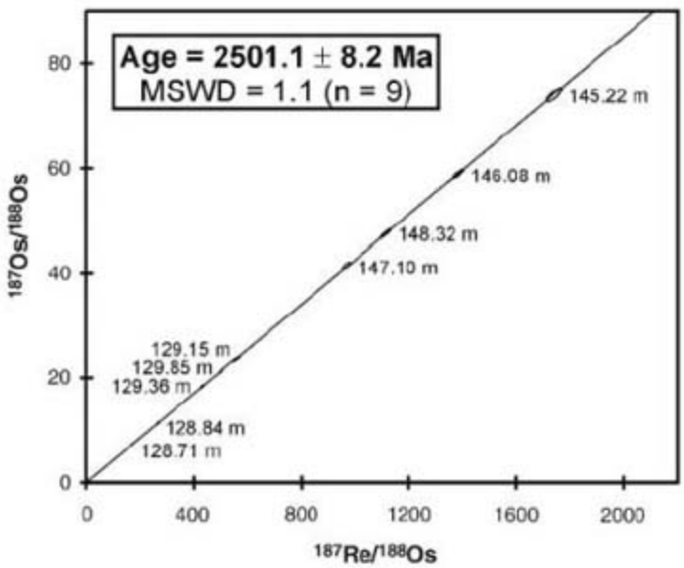

Fig. 2. Re/Os isochron from the Mount McRae Shale, based on data from two subintervals within S1 (128.71 to 129.85 m and 145.22 to 148.32 m). MSWD, mean square weighted deviation. The Re/Os age, 2501.1 ± 8.2 Ma (initial $^{187}Os/^{188}Os$ = 0.04 ± 0.06), falls between prior ages of 2479 ± 3 Ma for the overlying Dales Gorge Member of the Brockman Iron Formation (*20*) and 2561 ± 8 Ma for the underlying Bee Gorge Member of the Wittenoom Formation (*21*). Details are discussed in (*22*).

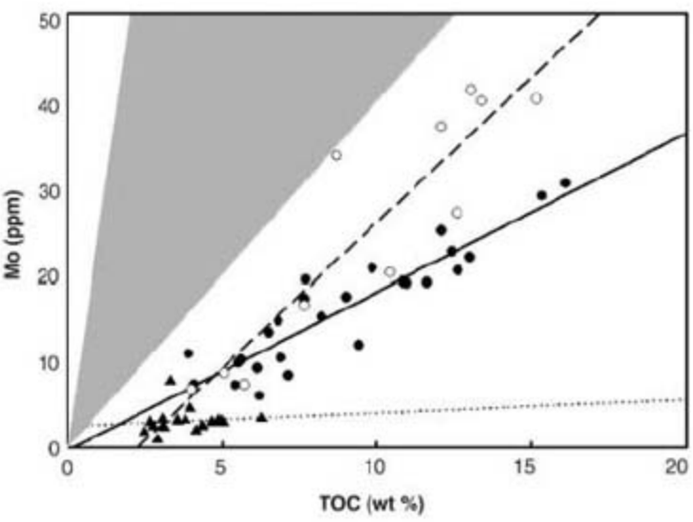

Fig. 3. Relationship between Mo and TOC in organic carbon-rich pyritic intervals in the Mount McRae Shale. Circles are from interval S1 (125.5 to 153.3 m). The metal-enriched zone of S1 below 143 m (open circles) is differentiated from the upper zone (solid circles). Triangles are from interval S2 (173.0 to 189.7 m). For comparison, the shaded region indicates the range of Mo/TOC slopes (forced through the origin) observed in modern sulfide-rich anoxic basins.

0.35 (±1σ) ppm Mo/wt % TOC] (Fig. 3). Weak correlations appear between Mo and Al in S2, suggesting that at these depths the Mo budget was influenced by detrital components; such correlations are absent from S1. These observations point to much less authigenic Mo enrichment in S2 than in S1.

The difference in Mo enrichment suggests that the Mo inventory in overlying waters was much larger during S1 deposition than during S2 deposition, as would follow from an increase in environmental oxygenation up the section beginning at ~153 m. This interpretation is complicated by the fact that the Mo concentration differences between the units were also affected by differences in local depositional conditions that increased the efficiency with which Mo was transferred from water to sediments during S1 time (*35*). However, a difference in the dissolved Mo inventory and in ocean oxygenation provides a compelling explanation for the sharp difference in Mo/TOC between the units (*36*).

Other data from the core also point to greater surface ocean oxygenation above ~153 m, including changes in $\delta^{34}S$-$\Delta^{33}S$ systematics that may record the onset of an oxidative sulfur cycle (*23*). A redox shift can also explain differences in Fe and Mn concentrations above and below ~160 m (Fig. 1). Below this depth, most of the Fe is present as siderite ($FeCO_3$), and both elements are much lower in S1 than in S2. Fe and Mn would have been easily mobilized during anoxic weathering, enriched in anoxic S-poor Archean oceans and hence available for incorporation into sediments. Oxygenation of surface environments would have reduced the availability of both elements. At the same time, Re concentrations are slightly elevated above crustal average values throughout the core, and there is a positive correlation of Re with TOC in S2 as well as S1 (fig. S2B). Re can be more mobile than Mo during oxidative sulfide weathering (*37*), so this persistent Re enrichment suggests that some small degree of oxidative weathering occurred throughout.

The decrease in Mo content and Mo/TOC above 143 m may record a drop in the dissolved Mo inventory after its initial rise, even though the surface environment apparently remained persistently, if mildly, oxygenated (*23*). Re and S also decrease. Diagenetic complications notwithstanding (*23*), it is tempting to speculate that these decreases mirror a drop in atmosphere or ocean redox potential (*38*), as a result of biological or nonbiological feedbacks (*39*). However, declining trace metal abundances could simply reflect the exhaustion of exposed crustal sulfide sources, or areal expansion of sulfidic basins in the oceans in response to rising sulfate reduction, drawing down seawater Mo, Re, and S inventories.

The onset of oxidative weathering at 2.5 Ga was probably widespread. A recent examination of contemporaneous sediments from the Ghaap Group in South Africa found that authigenic Mo and Re increased between 2.64 and 2.5 Ga (*40*), although that study did not have the stratigraphic resolution to capture the scale of variations reported here. Changes in S isotope systematics like those in the Mount McRae Shale also appear in time-correlative units from South Africa (*23*). Theoretical models show that a shift toward more oxidizing conditions can occur before the rise of an oxygenated atmosphere (*5*). Hence, the whiff of oxygen in the Mount McRae Shale may presage the global and irreversible transition to an oxygenated world.

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28. The duration of S1 is difficult to estimate but is <16 million years based on the uncertainty in the Re/Os isochron. Assuming a typical average shale accumulation rate of ~2.5 m/million years, the duration is ~11 million years. These estimates are consistent with accumulation rates determined from prior geochronology of sampled units (*20*, *21*).
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39. For example, biologically, rising O_2 could inhibit N_2 fixation or limit the availability of bioessential Fe, thereby reducing productivity and the rate of O_2 production. Nonbiologically oxidative erosion of a methane greenhouse would lead to lower surface temperatures, hence higher solubility of O_2 in surface oceans, lowering P_{O_2}.
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Supporting Online Material

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Materials and Methods
Figs. S1 and S2
Tables S1 to S3

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Stone Adze Compositions and the Extent of Ancient Polynesian Voyaging and Trade

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The last region on Earth settled by humans during prehistory was East Polynesia. Hawaiian oral histories mention voyaging from Hawai'i to Tahiti and back via the Tuamotus, an open ocean journey of several thousands of kilometers. The trace element and isotope chemistries of a stone adze recovered from the Tuamotu Archipelago are unlike those of sources in central Polynesia but are similar to the Kaho'olawe Island hawaiite, in the Hawaiian Islands, supporting the oral histories. Other adzes collected from the low coral islands of the northwest Tuamotus have sources in the Marquesas, Austral and Society Islands, and the Pitcairn Group, confirming that trade was widespread within East Polynesia.

The greatest maritime migration in human history culminated in the settlement of the eastern margins of the Pacific Ocean, delimited by Hawai'i, New Zealand, and Easter Island, the last region on Earth to be settled by humans. Some researchers have suggested that settlement was accidental or by drift voyages (*1*). However, computer simulations (*2*, *3*), sailing experimental canoes using traditional navigational techniques (*4*), and review of voyaging strategies (*2*) indicate that East Polynesian colonization was purposeful, perhaps taking about six human generations to colonize most archipelagoes before 900 CE (*5*).

In the eastern Pacific, the decreasing island size and isolation of archipelagoes across Polynesia made it difficult to maintain external relations among them, and the frequency of long-distance voyaging is thought to have diminished (*6*). However, two-way postcolonization voyaging between Hawai'i and Tahiti is well supported by Hawaiian oral histories (*7*).

To evaluate the extent of trade in eastern Polynesia, we studied the trace element compositions and isotope chemistry of exotic stone adzes collected from nine coral atolls in the Tuamotus: the navigational crossroads of East Polynesia (*2*) (Fig. 1, A and B). These adzes are made of basalt, for which there is no local source on the coral atolls. Thus, their provenance can be used to trace Polynesian travel and trade. To evaluate sources, we developed a database containing major, trace element,

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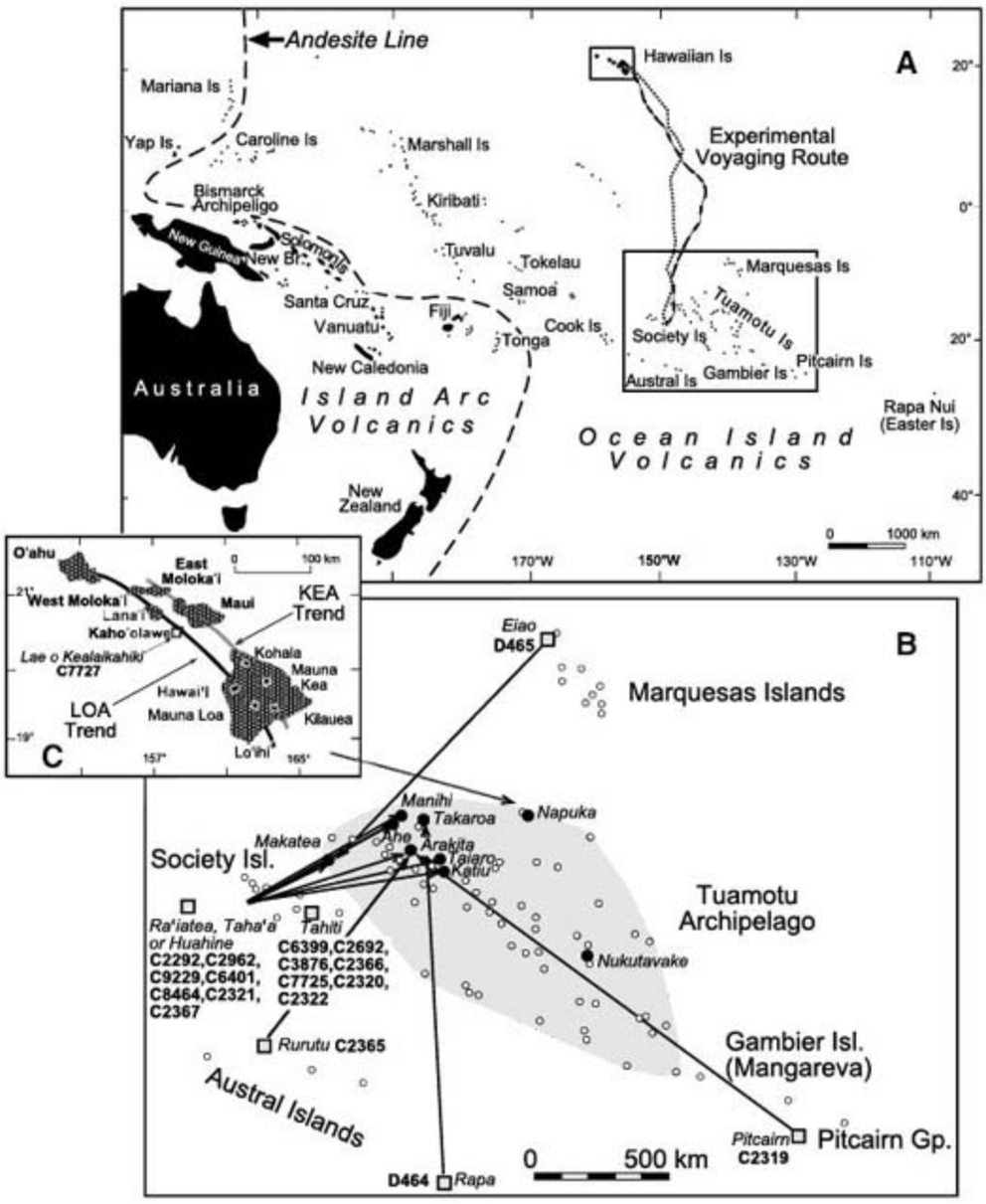

Fig. 1. (**A**) Pacific islands showing OIBs (east of the Andesite Line), IAVs, and the route between Hawai'i and Tahiti within the Society Islands established experimentally (*4*). (**B**) The distribution of adzes investigated in our study. Arrows link adze locations (solid circles) to their sources (gray squares) in the Marquesas, Society, Austral, Tuamotu, Gambier, and Pitcairn Island groups. (**C**) The Hawaiian Islands, with contemporary vents on Hawai'i and Lo'ihi designated with black circles. The two linear trends (Loa and Kea) define distinctive chemical and isotopic differences within the Hawaiian mantle plume (*27*).

Table 1. Major element compositions (in weight %), selected trace element ratios, and isotopic compositions of adzes and source basalts.

	Artifact	Rurutu	A/S*	Artifact	Eiao	A/S	Artifact	Pitcairn	A/S	Artifact	Societies	A/S	Societies	A/S	Artifact	Kaho'olawe	A/S
	C2365	KC-05-1		D465	KC-05-11		C2319	KC-05-13		C2367	Taha'a 1Ta-2V‖		Ra'iatea KC-05-21		C7727¶	H-1440#	
SiO_2	43.23	46.98	0.92	45.23	47.83	0.95	49.85	51.27	0.97	46.53	44.72	1.04	45.38	1.03	46.76	50.34	0.93
TiO_2	4.29	3.15	1.36	3.90	3.96	0.98	2.84	2.73	1.04	3.26	3.12	1.05	4.64	0.70	4.65	3.08	1.51
Al_2O_3	14.73	16.16	0.91	15.66	15.44	1.01	15.88	15.41	1.03	12.70	12.96	0.98	16.02	0.79	14.75	16.62	0.89
FeO	15.42	13.27	1.16	13.12	12.06	1.09	12.30	11.99	1.03	11.56	11.87	0.97	11.24	1.03	12.00	10.81	1.11
MnO	0.23	0.22	1.06	0.21	0.17	1.28	0.21	0.21	1.01	0.18	0.20	0.90	0.17	1.08	0.18	0.17	1.01
MgO	6.11	4.45	1.37	5.04	6.41	0.79	3.62	3.50	1.03	8.17	9.97	0.82	5.83	1.40	4.90	4.70	1.04
CaO	8.35	7.37	1.13	10.82	9.22	1.17	7.25	7.04	1.03	13.21	12.14	1.09	10.15	1.30	10.44	6.82	1.53
Na_2O	4.57	5.56	0.82	3.35	3.33	1.01	4.62	4.57	1.01	2.62	3.66	0.71	3.32	0.79	3.11	4.74	0.66
K_2O	1.78	1.67	1.07	1.89	1.05	1.80	2.07	1.99	1.04	1.28	0.76	1.68	2.22	0.58	2.43	1.86	1.30
P_2O_5	1.31	1.17	1.11	0.77	0.54	1.44	1.36	1.30	1.05	0.49	0.60	0.81	1.0	0.48	0.79	0.86	0.92
Total	100.0	100.0		100.0	100.0		100.0	100.0		100.0	100.0		100.00		100.0	100.00	
Rb/Sr	0.036	0.029	1.25	0.040	0.037	1.10	0.080	0.066	1.22	0.050	0.067	0.75	0.050	1.02	0.051	0.050	1.06
Sm/Nd	0.188	0.186	1.01	0.243	0.249	0.98	0.214	0.214	1.00	0.220	0.210	1.05	0.208	1.06	0.216	0.229	0.94
U/Pb	0.59	0.65	0.91	0.41	0.43	0.95	0.34	0.37	0.92	0.36	0.55	0.65	0.26	1.37	0.27		
Th/Pb	2.08	2.28	0.91	1.35	1.42	0.95	1.36	1.52	0.89	1.15	2.20	0.52	0.91	1.27	0.90		
Ba/Th	53.8	51.8	1.04	64.7	66.2	0.98	73.7	74.3	0.99	106.1	105.5	1.01	101.6	1.04	108.5	125.1	0.87
Zr/Hf	47.8	46.8	1.02	42.5	42.3	1.00	44.0	42.5	1.04	41.4	43.0	0.96	45.0	0.92	42.7	43.4	0.98
Nb/Ta	16.9	17.4	0.97	15.7	15.8	0.99	16.6	16.6	1.00	16.2	17.4	0.94	16.9	0.96	16.2	15.8	1.02
Nb/Th	14.4	11.5	1.25	9.9	9.8	1.00	11.6	11.6	1.00	13.4	10.5	1.28	10.2	1.31	13.1	11.9	1.10
$^{87}Sr/^{86}Sr$†	0.70330	0.70352		0.70400	0.70394		0.70360	0.70357		0.70414	0.70374		0.70440		0.704069	0.70426	
$^{143}Nd/^{144}Nd$‡	0.512933	0.512937		0.512943	0.512953		0.512820	0.512826		0.512896	0.512890		0.512894		0.512897	0.512864	
$^{206}Pb/^{204}Pb$	20.289 ± 0.018	20.332 ± 0.015		19.133 ± 0.014	19.132 ± 0.019		18.437 ± 0.026	18.455 ± 0.009		18.792 ± 0.010	18.766		18.873 ± 0.011		18.060 ± 0.004	18.005	
$^{207}Pb/^{204}Pb$	15.674 ± 0.014	15.718 ± 0.013		15.552 ± 0.011	15.576 ± 0.017		15.488 ± 0.021	15.497 ± 0.007		15.563 ± 0.009	15.480		15.602 ± 0.009		15.495 ± 0.003	15.447	
$^{208}Pb/^{204}Pb$	39.760 ± 0.036	39.912 ± 0.036		38.852 ± 0.029	38.915 ± 0.041		38.948 ± 0.054	38.996 ± 0.019		38.496 ± 0.029	38.301		38.699 ± 0.025		37.698 ± 0.011	37.817	
$^{207}Pb/^{206}Pb$	0.7726 ± 0.0001	0.7731 ± 0.0001		0.8128 ± 0.0001	0.8141 ± 0.0002		0.8401 ± 0.0002	0.8397 ± 0.0001		0.8291 ± 0.0001	0.8249		0.8267 ± 0.0001		0.8580 ± 0.0001	0.8579	
$^{208}Pb/^{206}Pb$	1.9597 ± 0.0003	1.9630 ± 0.0005		2.0306 ± 0.0004	2.0340 ± 0.0005		2.1127 ± 0.0004	2.1130 ± 0.0002		2.0508 ± 0.0003	2.0410		2.0505 ± 0.0002		2.0875 ± 0.0002	2.1004	
$^{208}Pb^*/^{206}Pb^*$§	0.936	0.947		0.954	0.961		1.038	1.041		0.951	0.933		0.964		0.939	0.959	
$^{207}Pb^*/^{206}Pb^*$§	0.490	0.492		0.535	0.538		0.569	0.569		0.556	0.548		0.555		0.594	0.593	

*The similarity of major and trace element data is shown by dividing artifact values by source compositions (A/S). †External reproducability in $^{87}Sr/^{86}Sr$ = 0.000025 (2σ). ‡External reproducability in $^{143}Nd/^{144}Nd$ = 0.000016 (2σ). §The $^{207}Pb^*/^{206}Pb^*$ and $^{208}Pb^*/^{206}Pb^*$ radiogenic Pb isotopic compositions were calculated by subtracting the following initial Pb isotope ratios: $^{206}Pb/^{204}Pb$ = 9.3066, $^{207}Pb/^{204}Pb$ = 10.293, and $^{208}Pb/^{204}Pb$ = 29.475 (*39*). ‖Basanite from Taha'a expresses as anhydrous composition (*40*, *41*). ¶Single analysis of C7727 with 5-V ^{208}Pb beam. The mean given in table S4 was determined using this data as well as two new mass spectrometer determinations using separate and progressively smaller Pb loads from the same chemistry. Mass spectrometer run no. 2 with a 1-V beam and no. 3 with a 100-mv beam yielded the following isotopic compositions: $^{206}Pb/^{204}Pb$ = 18.020 ± 0.009 and 17.913 ± 0.048; $^{207}Pb/^{204}Pb$ = 15.940 ± 0.028 and 15.450 ± 0.043; $^{208}Pb/^{204}Pb$ = 37.708 ± 0.028 and 37.594 ± 0.101; $^{207}Pb/^{206}Pb$ = 0.8573 ± 0.0002 and 0.8580 ± 0.0022; $^{208}Pb/^{206}Pb$ = 2.0855 ± 0.0004 and 2.0918 ± 0.0045; $^{208}Pb^*/^{206}Pb^*$ = 0.945 and 0.943; and $^{207}Pb^*/^{206}Pb^*$ = 0.597 and 0.595. #Post-caldera hawaiite (*24*). The Ba/Th ratios for Kaho'olawe lavas range from 60 to 450, mean = 136 ± 89 (n = 36 analyses) (*42*).

and isotopic compositions of 28 volcanic sources from all Polynesian archipelagos, augmented by data (*8*) for oceanic island basalts (OIBs). Fine-grained basalt adzes and their resulting manufacturing debris occur throughout Polynesia, and this common woodworking tool has been used to identify prehistoric interaction between island groups (*9*, *10*).

Island arc volcanics (IAVs) and OIBs are chemically distinct because of differences in mantle sources and melting processes (*11*). The IAVs west of the Andesite Line (Fig. 1A) comprise volcanic rocks that range with increasing silica from basalt to andesite, dacite, and rhyolite. These IAVs form by melting of the hydrated mantle wedge above subduction zones (*12*). The range of silica in these magmas reflects fractional crystallization within high-level magma chambers and the assimilation of overlying felsic crust (*13*). By contrast, tholeiitic and alkalic OIBs and associated silica-undersaturated alkaline lavas (*8*) (fig. S1) form by partial melting in mantle away from subduction zones (*14*). The movement of overlying oceanic lithospheric plates across mantle upwellings or loci of melting explains the generation of lines of OIB volcanoes, with ages increasing in the direction of plate movement away from the hot spot (*15*), as at Hawai'i (*16*). In eastern Polynesia, the Tuamotus, Marquesas, Society Islands, and Cook-Austral Islands, (Fig. 1B) are interpreted to have formed by this process (*17*).

Because of differences in mantle sources and melting processes, IAVs are chemically distinct from OIBs (*18*), and this difference provides a robust constraint for identifying the provenance of Polynesian basalt adzes. In addition, OIB lavas from different archipelagos exhibit different trace element and radiogenic isotope chemistries (*19*); such data can also be used to determine artifact sources. Major element chemistries may often not be diagnostic because similar basalt chemistries can be produced during the fractional crystallization of similar mineral phase sequences during cooling in high-level magma chambers.

OIBs are characterized by superchondritic Zr/Hf ratios (chondritic ratio 34.3 ± 0.3) and subchondritic Nb/Ta ratios [chondritic ratio 19.9 ± 0.6 (*20*)]. Furthermore, OIBs exhibit low and distinctive superchondritic Zr/Hf ratios of 35.5 to 43.5 [chondritic ratio 34.3 ± 0.3 (*20*)]. An additional method for discriminating between basalts is provided by radiogenic Sr, Nd, and Pb isotope compositions, for which there are extensive data for Polynesian volcanoes (*8*, *21*). Initial isotopic compositions of OIBs are diverse (*8*). In view of the marked trace element and isotopic differences between different OIB archipelagos, sources of basalt used in adze manufacture can be determined without requiring knowledge of specific locations of sources or quarries.

We analyzed 19 adzes collected by Emory between 1929 and 1934 (*8*, *22*) (table S1) from nine low coral atolls (Arakita, Makatea, Napuka, Takaroa, Katiu, Manihi, Ahe, Taiaroa, and Nukutavake) (Fig. 1, A and B). They are typical East Polynesian adze forms (Duff types 1A, 1E, 3A, 3B, 4A, and 5B) (*23*), with types 3A and 4A representing late prehistoric forms (fig. S1). These artifacts, analyzed by inductively coupled plasma mass spectrometry and with radiogenic isotope ratios analyzed by thermal ionization mass spectrometry, required <100 mg of sample (*8*) (table S2).

The radiogenic isotopic data (Table 1 and Fig. 2) allow three adzes to be assigned to their sources; C2365 from Rurutu, C2319 from Pitcairn, and C7727 with an isotopic composition indicating derivation from Kaho'olawe, Hawai'i. C7727 is a phenocryst-free aphanitic rock (fine-grained, where mineral phases are not discernable with the naked eye) that is typical of rocks selected for adze making. The unradiogenic Pb isotopic composition of C7727 is distinct from those of all other

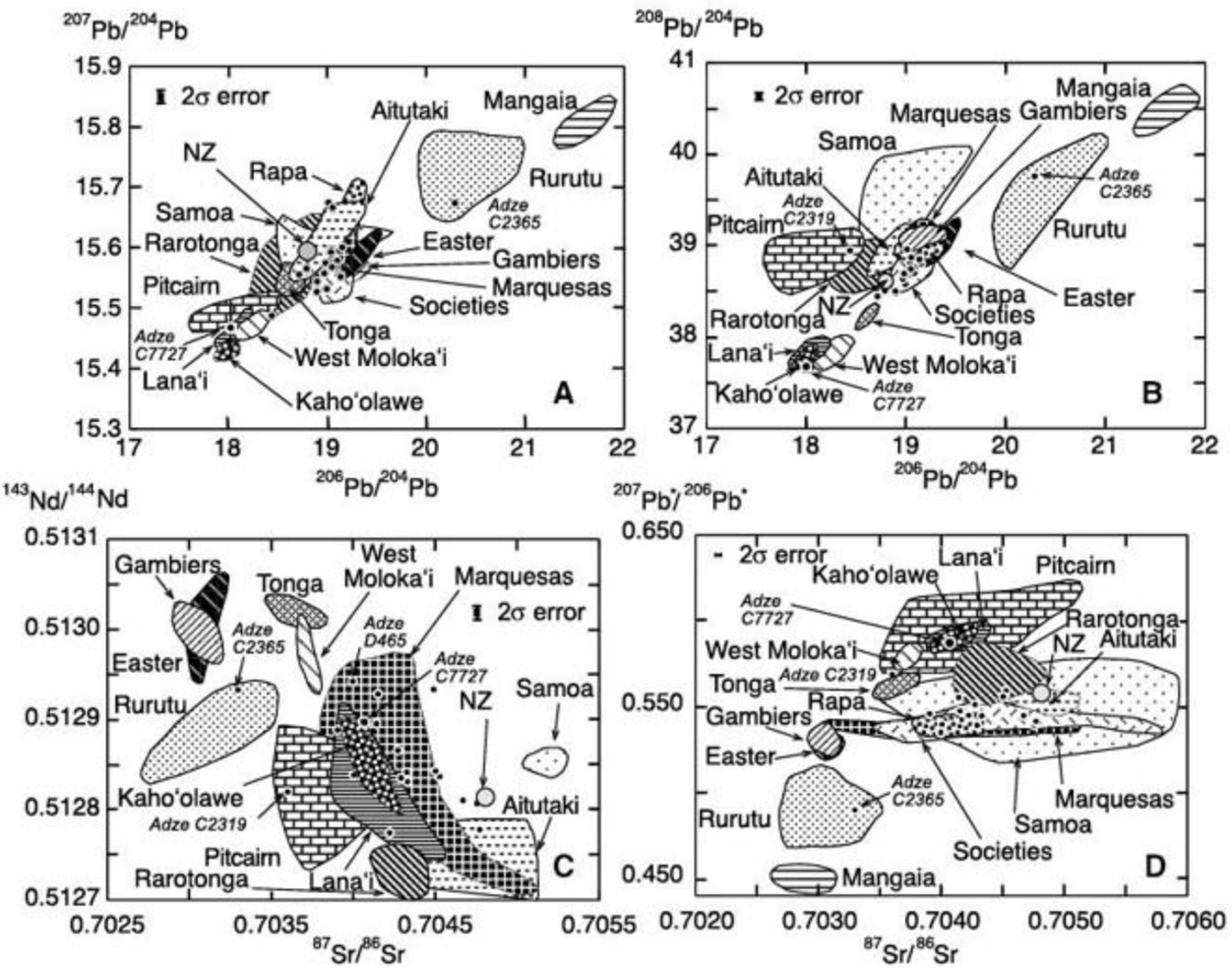

Fig. 2. (**A** to **D**) Isotopic compositions of adzes (solid circles) and compositional fields for different Polynesian OIBs. Source fields are defined by data in table S5 and studies cited in (*8*). Variations in isotopic composition define the nature and scale of chemical heterogeneity within mantle sources of OIBs (*11*). Radiogenic Pb isotopic compositions of adzes shown in Fig. 3, A and B, reflect variation in U/Pb ($^{206}Pb/^{204}Pb$ and $^{207}Pb/^{204}Pb$) ratios and also in Th/Pb ($^{208}Pb/^{204}Pb$) ratios. Figure 3C shows covariation between Sr isotopic composition and Nd isotopic compositions. Figure 3D shows covariation between $^{207}Pb^*/^{206}Pb^*$ and $^{87}Sr/^{86}Sr$ ratios. Based on isotopic composition, three adzes can be assigned to their sources: C2365, Rurutu; C2319, Pitcairn; and C7727, Hawai'i [using the average of three Pb isotope determinations given in Table 1 and the sixth footnote of Table 1 (designated by ¶). The unradiogenic Pb isotopic composition of C7727 is distinctive from that of all other eastern Polynesian OIBs and is similar to Loa trend basalts (Fig. 1C). Although isotopically similar, Lana'i basalts are tholeiitic, whereas C7727, a hawaiite (fig. S1), is from Kaho'olawe. Error bars show 2σ analytical uncertainties in each diagram.

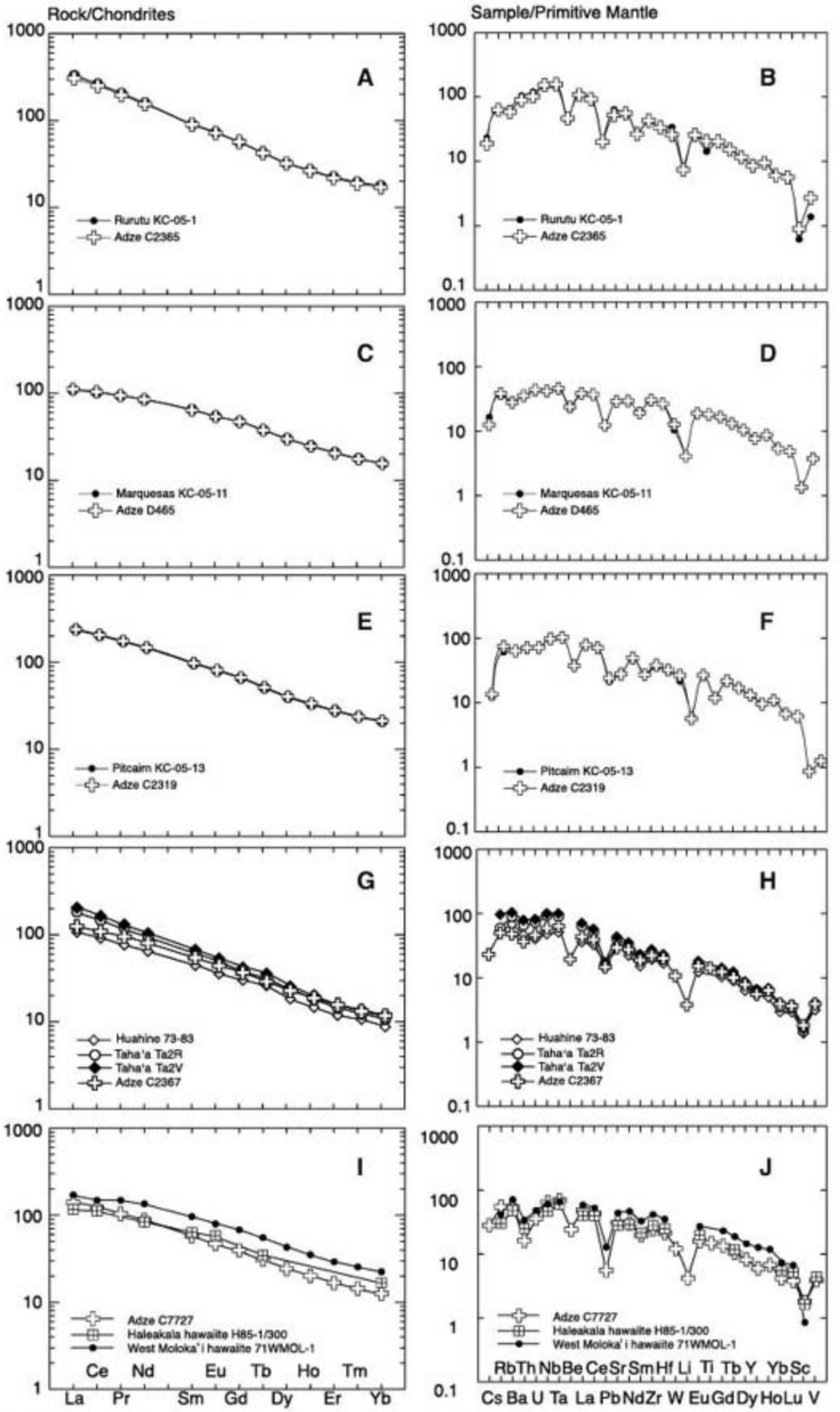

Fig. 3. Geochemical comparisons. (**A** and **B**) Similarity between C2365 and Rurutu basalts. (**C** and **D**) Similarity between D465 and the Eiao source, Marquesas. (**E** and **F**) Similarity between C2319 and Tautama basalt, Pitcairn Island. (**G** and **H**) Similarity between C2367 and basalts from Huahine and Taha'a in the Society Islands with high Ba/Th ratios. (**I** and **J**) Comparison between adze C7727 and hawaiites with similar SiO_2 composition from West Moloka'i (71WMOL-4) (*28*) and Haleakala, Maui (H85-1) (*29*). The similarity between C7727 and Haleakala hawaiite indicates that they had a common petrogenetic evolution.

eastern Polynesian OIBs but is similar to either Kaho'olawe or Lana'i (*24*–*26*). Both of these islands lie in the Hawaiian Loa trend (*27*) (Fig. 1C). Although Lana'i basalts are isotopically similar to those on Kaho'olawe, they are tholeiitic, whereas C7727, a hawaiite, is alkalic (fig. S2). Adze C7727 (table S4) has similar SiO_2, Al_2O_3, MgO, TiO_2, Fe_2O_3, and P_2O_5 compositions to hawaiites from West Moloka'i and Haleakala, Maui (*28*, *29*) (table S5). Fig. S3A shows that hawaiites from Haleakala and West Moloka'i have considerable variation in CaO (5.4 to ~10 weight %).

Adze C7727 has similar CaO and TiO_2 compositions to Ca-rich hawaiites from Haleakala, confirming a common petrogenetic evolution, different from hawaiites from Mauna Kea and West Moloka'i. Adze C7727 falls within the field of covariation exhibited by other hawaiites from Hawai'i in plots of MgO with Nb, Sr, and Th (fig. S4) and with CaO/Na_2O, Nb/Th, Th/Ta, and Nb/Ta ratios (fig. S5). The adze has a similar CaO/Na_2O ratio to high-Ca hawaiites from Haleakala, Maui (fig. S5). However, its Pb isotopic composition excludes West Moloka'i (*28*) or Maui (*30*) hawaiite as a source for this adze.

In Sr/Ce versus P_2O_5 space, adze C7727 plots within the distinctive range of compositions exhibited by hawaiites from Kaho'olawe (fig. S6). Such variation reflects both shallow low-pressure fractionation of plagioclase (as in Haleakala, Maui hawaiites) and moderate-pressure fractionation of clinopyroxene (as in West Moloka'i and Mauna Kea hawaiites) (*29*). Furthermore, Kaho'olawe hawaiites are also characterized by higher Ni contents (range 54 to 226, 143 ± 71 μg/g) (*24*, *31*) than hawaiites from West Moloka'i (1 to 40 μg/g) (*28*), Haleakala (4.5 to 51 μg/g) (*29*), and Mauna Kea (4 to 9 μg/g) (*32*). With 115 μg of Ni/g, adze C7727 is consistent with derivation from a hawaiite source on Kaho'olawe.

Further support for the idea that C7727 originated from Hawai'i is provided by trace element ratios and by Sr and Nd isotope ratios given in Table 1, tables S4 and S5, Fig. 3, and fig S7. OIBs from Hawai'i and almost all basalts from the Emperor Seamont chain, which represents Hawaiian magmatism ranging in age from 85 to 42 million years ago, have Ba/Th ratios >100 (*33*). In East Polynesia, basalts from Ra'iatea (table S5) and Taha'a (*34*) in the Society Islands, shown in Fig. 3, G and H, also have Ba/Th ratios >100; however, basalts from the Society Islands have significantly higher radiogenic Pb isotopic compositions than those from Hawai'i (Fig. 2B, Table 1, and table S5). Although the La/Yb ratio of C7727 (16.5) (table S4) is higher than published values for Kaho'olawe lavas, the rare earth elements are especially mobile because of alteration in some post-shield alkalic lavas (*31*). The La/Yb ratio is also affected by the degree of partial melting; thus, the higher ratio of C7727 reflects a lower degree of melting. In $^{87}Sr/^{86}Sr$ and $^{143}Nd/^{144}Nd$ space (fig. S7), adze C7727 plots within the Kaho'olawe field on a mixing trend (correlation coefficient $R = 0.97$) defined by hawaiites from Kaho'olawe, West Moloka'i, and Haleakala (Maui). This indicates that a com-

mon petrogenetic process was involved in hawaiite formation. This most likely involved interaction between an enriched component with a high Rb/Sr ratio and low Sm/Nd ratio and a depleted component with a lower Rb/Sr ratio and higher Sm/Nd ratio.

We used the same methodology (Table 1 and Figs. 2 and 3) to identify the sources of all 19 adzes. In addition to the adzes from Kaho'olawe, Hawai'i ($n = 1$); the Pitcairn Group ($n = 1$), and Rurutu ($n = 1$), adzes were also identified that were manufactured from basalt sources on Eiao in the Marquesas ($n = 1$); Rapa in the Australs ($n = 1$); the Society Islands with Ba/Th ratios >100, such as Ra'iatea, Taha'a, or Huahine ($n = 7$); and the Society Islands with Ba/Th ratios <100, such as Tahiti ($n = 7$).

Because adze C7727 was collected from Napuka, a low coral atoll in the western Tuamotus in central East Polynesia (Fig. 1B), the rock from which it was made was transported a minimum distance of 4040 km from its source on Kaho'olawe in the Hawaiian chain (Fig. 1A). The likely route between Hawai'i and Tahiti via the Tuamotus (*35*) (Fig. 1A) has favorable winds and currents for two-way voyages. Experimental canoes using non-instrumental navigation made such a journey in 32 days (*36*).

There is much traditional ceremony in preparation for long-distance voyaging, and today, as possibly in the ancient past, canoeists often stop at the westernmost tip of Kaho'olawe Island, Lae o Kealaikahiki (literally, "cape or headland of the way to Tahiti") (Fig. 1C) before beginning their voyage south. Sample C7727, a Duff type 3A adze, is made from rock that is consistent with hawaiite deposits found at only a few places along the coast of this island, one of which is close to Lae o Kealaikahiki. This adze type is unknown from Hawai'i but is common in the Tuamotus. Rock from Kaho'olawe may thus have been taken as a gift or memento (as is done today by modern traditional voyagers) or used as ballast, and fashioned into adzes in the Tuamotus.

The Tuamotus, along with the Society Islands, could be approached from all quarters and was thus probably important in Polynesian trade (*2*). Our data show that Tuamotu adzes originate from the Marquesas, Pitcairn, Austral, and Society Islands; that is, most of the island groups surrounding the atoll archipelago. Furthermore, because the low coral atolls of the Tuamotus emerged after 1200 CE (*37*), and the surrounding island groups were colonized well before then, all imported adzes recovered in the Tuamotus relate to postcolonization interaction with adjacent archipelagoes. We therefore agree with Irwin (*2*) that postcolonization voyaging must have been common enough for voyaging knowledge to be passed across generations and that it continued until about 1450 CE when most voyaging ceased in East Polynesia (*38*).

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Materials and Methods
SOM Text
Figs. S1 to S7
Tables S1 to S5
References

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Synchrony Dynamics During Initiation, Failure, and Rescue of the Segmentation Clock

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The "segmentation clock" is thought to coordinate sequential segmentation of the body axis in vertebrate embryos. This clock comprises a multicellular genetic network of synchronized oscillators, coupled by intercellular Delta-Notch signaling. How this synchrony is established and how its loss determines the position of segmentation defects in Delta and Notch mutants are unknown. We analyzed the clock's synchrony dynamics by varying strength and timing of Notch coupling in zebrafish embryos with techniques for quantitative perturbation of gene function. We developed a physical theory based on coupled phase oscillators explaining the observed onset and rescue of segmentation defects, the clock's robustness against developmental noise, and a critical point beyond which synchrony decays. We conclude that synchrony among these genetic oscillators can be established by simultaneous initiation and self-organization and that the segmentation defect position is determined by the difference between coupling strength and noise.

The periodic and sequential segmentation of the vertebrate embryo along its anterior-posterior axis into blocks of cells called somites, the precursors of axial bone and muscle, is thought to be driven by the segmentation clock (Fig. 1A) (*1*, *2*). This clock com-

prises a multicellular genetic network of oscillators located within the posterior mesoderm (Fig. 1B) (*3*, *4*). Delta-Notch signaling has been proposed (*3*, *5*) to couple these oscillators (Fig. 1C) such that they are spatiotemporally synchronized despite the presence of noise. Desynchronization over developmental time (*5*) could explain the zebrafish Delta-Notch mutant phenotypes (*6*–*10*) in which only the first 6 to 10 anterior segments form correctly (*11*); alternatively, genetic differences in anterior and posterior patterning might set the positions of these segmentation defects (*11*, *12*). A physical theory that accounts for these defect positions based on desynchronization dynamics and Delta-Notch signaling strength is lacking, and how this clock is started and attains initial synchrony is also unknown.

If desynchronization is the cause of Delta-Notch mutant phenotypes, such a decay process should be inducible throughout somitogenesis. We delivered saturating doses of N-[N-(3,5-difluorophenacetyl-L-alanyl)]-S-phenylglycine t-butyl ester (DAPT) to wild-type (WT) embryos at hourly intervals (*13*). DAPT binds to and blocks the intramembrane protease required for cleavage of the Notch intracellular domain in response to Delta binding the receptor's extracellular domain (Fig. 1D) (*14*). We quantified the resulting organismal phenotype with the anterior limit of defects (ALD) (Fig. 1E), that is, the number of the anterior-most defective segment (*15*), which, averaged over an embryo population, is characteristic for each mutant (*11*, *15*) and is indicated by the myotome boundary marker cb1045 (*16*). The ALD of fixed embryos translated into the developmental time, t, of the first misformed segment boundary (Fig. 1F) because segments formed at a linear rate

$$S = \alpha \cdot t - \mu \qquad (1)$$

with segment number S, segmentation rate $\alpha = 2.5 \pm 0.25$ hour^{-1}, and offset $\mu = 25 \pm 3$ ($N = 6$ embryos) (mean ± uncertainty = 2 SEM and 95% confidence unless stated otherwise). DAPT delivered before $t_0 = 5.8 \pm 0.5$ hours caused a constant ALD of $S_{ALD}^{-/-} = 5.2 \pm 0.18$ ($N = 31$), whereas later delivery shifted the ALD posteriorly (Fig. 1, E and F). These data are consistent with a decay process underlying the Delta-Notch mutant phenotype, and, assuming near-instantaneous action of DAPT treatment, t_0 would mark the beginning of this process with a decay time of 6.5 hours.

Furthermore, if desynchronization is the cause of Delta-Notch phenotypes, this decay time should be modifiable. We blocked Notch signaling before t_0 in WT and *des*$^{+/-}$ (*notch1a* heterozygote mutant) (*7*), varying (i) DAPT concentrations to reduce Notch activation and (ii) antisense morpholino (MO) amounts to reduce translation of *notch1a* mRNA (Fig. 1D) (*7*, *13*). Both treatments for quantitative perturbation of gene function gave consistent results (Fig. 2, A and B): The ALD shifted posteriorly with lower treatment levels, and curves for *des*$^{+/-}$ and WT shifted along the treatment axis, requiring about half the amount of treatment in *des*$^{+/-}$ to achieve the same effect as WT, suggesting a 0.5-fold difference in signaling. Saturating MO amounts caused an ALD consistent with *des*$^{-/-}$, $S_{ALD}^{-/-} = 7.63 \pm 0.12$ ($N = 108$) (*11*), whereas saturated DAPT concentrations caused lower ALDs, as above (Fig. 1, E and F), potentially because of DAPT targeting additional Notch receptors (*17*). Consequently, intercellular Delta-Notch signaling here is not simply a qualitative on-or-off switch; instead it can transmit smoothly graded quantitative signals, and this signal strength sets the decay time.

We sought a physical theory describing the dynamics of synchrony in the segmentation clock that predicts the first defective segment boundary S_{ALD} (=ALD) from the treatment level, n. We consider the segmentation clock as a population of identical, mutually coupled phase oscillators in the presence of noise (*13*, *18*), thereby neglecting the spatial aspects of cyclic gene wave patterns (*2*, *4*) and the biochemical details and amplitudes of the postulated cell-autonomous Her-feedback oscillators (*19*). We then described the synchrony among oscillating cells in mean-field approximation (Fig. 2C) (*13*) by an order parameter Z, with $Z = 0$ and $Z = 1$ for none and perfect synchrony, respectively (*18*). Below the threshold Z_c, proper segment formation fails (Fig. 2D). The dynamics of Z approximate an exponential (*18*) starting at t_0

$$Z(t) = Z(t_0) \cdot e^{-\lambda(t-t_0)/2} \qquad (2)$$

with the time constant

$$\lambda = 2\sigma^2 - \varepsilon \qquad (3)$$

determined by the antagonistic influence of the total noise experienced by the clock, $2\sigma^2$, and coupling among cells, ε. $2\sigma^2$ comprises environmental sources, like temperature fluctuations; intracellular sources, like cell division (*3*–*5*); and intercellular sources, like relative cell movements in the PSM mixing cells from regions with different phases (*5*). ε depends linearly on activated Notch protein level, p

$$\varepsilon = \beta \cdot \bar{p} + A \qquad (4)$$

where A accounts for potential additional coupling pathways. The sign of λ then determines whether synchrony decays or builds up, depending on whether noise or coupling dominates, respectively, and its magnitude determines the duration of either process. Hence at $\lambda = 0$ the collective behavior of these coupled oscillators undergoes a dramatic qualitative change, which marks the critical point at a synchronization phase transition (*18*, *20*, *21*), analogous to the freezing point at the water-ice transition (*13*).

A Hill equation accounts for the inhibitory effect of treatment level, n, with MO and DAPT assumed to act noncooperatively

$$\bar{p} = \delta \cdot \bar{p}_{WT} \cdot \left(1 - \frac{n}{n + n_0}\right) \qquad (5)$$

and where $2\delta = [0, 1, 2]$ is the number of *notch1a* alleles per embryo, $\bar{p}_{WT}$ is the WT level of activated protein, and n_0 is the treatment level that halves $\bar{p}_{WT}$. When applied to WT, n_0 would then correspond to the heterozygous condition.

Combining Eqs. 1 to 5 yields an expression that predicts the ALD of the homozygous mutant

$$S_{ALD}^{-/-} = (\alpha \cdot t_0 - \mu) - 2 \cdot \alpha \cdot \ln[Z_c/Z(t_0)]/(2\sigma^2 - A) \qquad (6)$$

which is set by the shortest decay time determined by the noise in the system to desynchronize cells in the absence of Notch signaling. More generally, we find the desired expression that predicts the ALD for any reduced Notch coupling strength due to the treatment level, n

$$S_{ALD} = \frac{S_{ALD}^{-/-} \cdot (n + n_0) - (\alpha \cdot t_0 - \mu) \cdot (n_{c,\delta} + n_0)}{n - n_{c,\delta}} \qquad (7)$$

Below the critical treatment

$$n_{c,\delta} = n_0 \cdot (\delta \cdot R - 1) \qquad (8)$$

in principle infinitely many correct segments could be formed. Here we define

$$R = \beta \cdot \bar{p}_{WT}/(2\sigma^2 - A) = \varepsilon_{WT}/(2\sigma^2 - A) \qquad (9)$$

as the robustness (*22*) of segmentation against changes in Notch signaling, other potential coupling pathways, and noise; a three-way balance that quantifies, for instance, the fold reduction in Notch signaling that is tolerable (*13*).

Fitting Eq. 7 to the data (Fig. 2, A and B) and with $S_{ALD}^{-/-}$ and t_0 fixed as above, we found the fit parameters for DAPT of $R = 8.6 \pm 2.2$ and $n_0 = 0.66 \pm 0.18$ μM and for MO, $R = 2.1 \pm 0.34$ and $n_0 = 0.021 \pm 0.005$ pmol; the resulting critical treatment levels, $n_{c,\delta}$, are marked in Fig. 2, A and B. Both values for R are larger than 2, hence consistent with the absence of a segmentation phenotype in the heterozygous mutant. These results provide quantitative evidence for (i) Notch signaling as a coupling mechanism, (ii) desynchronization as the cause of the Delta-Notch mutant phenotype, (iii) the system's robustness of $R \sim 5$, and (iv) the

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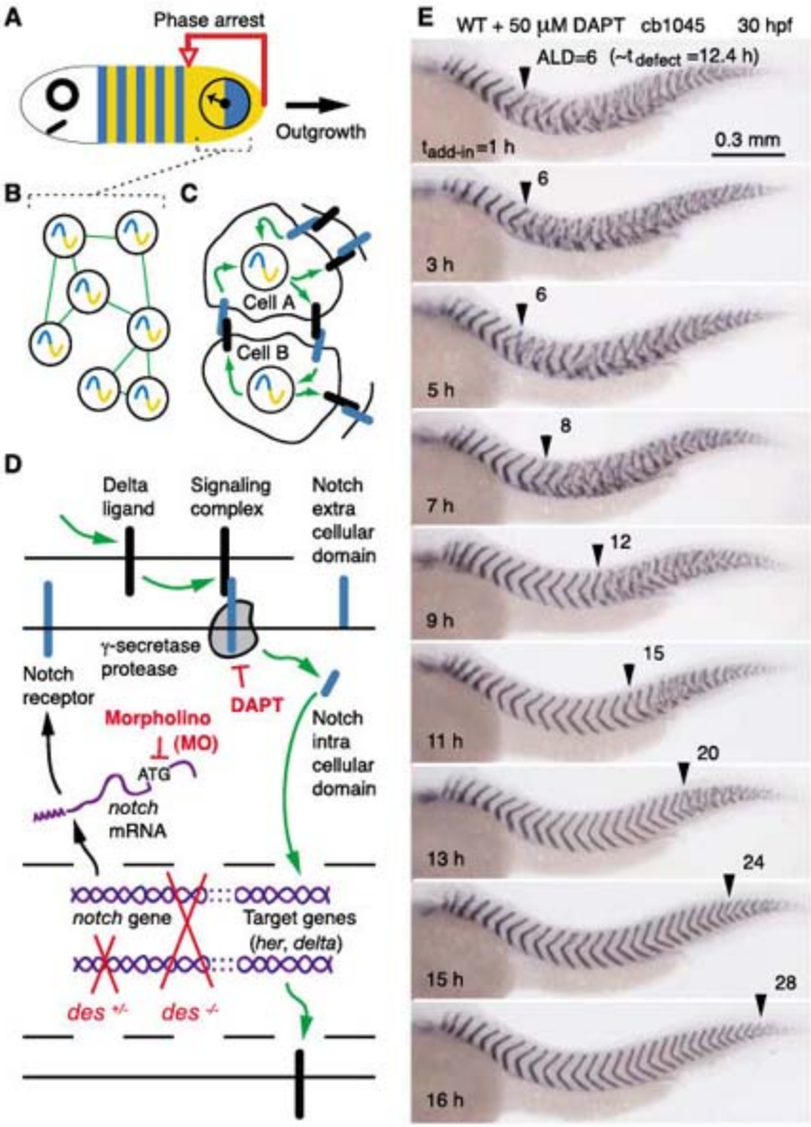

Fig. 1. A decay process within the segmentation clock underlies the Delta-Notch mutant segmentation phenotype. **(A)** Oscillation phase of the zebrafish segmentation clock (blue-yellow) in the outgrowing PSM is continuously imprinted at constant distance from the posterior end via a signaling gradient (*32*), providing cues for successive morphological body segmentation along the anterior-posterior axis. Perturbations in this pattern, i.e., insufficient coherence among oscillators, result in defective segment boundaries. **(B)** Network of genetic oscillators within PSM. **(C)** Mutual coupling via Delta-Notch signaling (green, signal transduction). Coupling acts to decrease phase differences between oscillators and opposes the phase-randomizing effects of noise. **(D)** Production, activation, turnover, and signaling of this pathway (*33*); treatments used in this study to reduce or completely block intercellular Delta-Notch coupling (red): MO, DAPT, and mutants in *notch1a* ($des^{+/-}$ and $des^{-/-}$). **(E)** Shifts in ALD of segment boundaries (arrowheads) from adding saturating DAPT levels at successively later times. **(F)** Functional representation of (E). Morphological ALD (left axis) converts into absolute time of defect (right axis). ALD error bars, ≥68% of scored embryos; solid line, linear fit; dashed lines, visual guidance marking saturating ALD, $S^{-/-}_{ALD}$, and decay onset time, t_0.

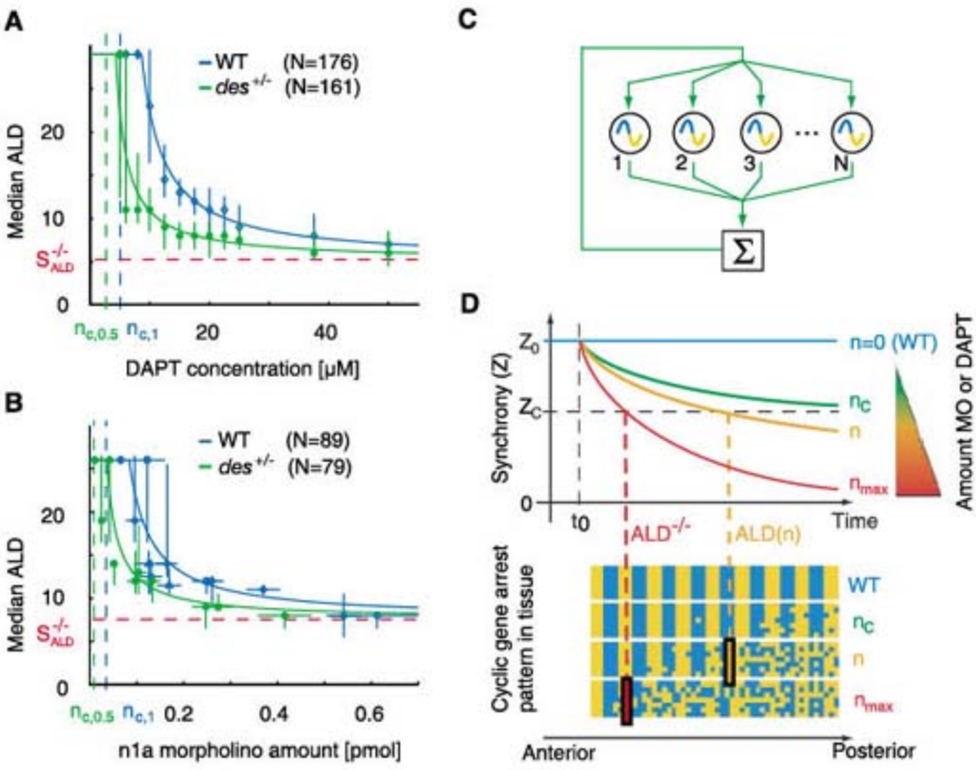

Fig. 2. A mean-field theory of coupled phase oscillators predicts the synchrony decay time in the segmentation clock and the segmentation defect position. **(A)** ALD resulting from various DAPT concentrations applied at dome stage to WT (blue) and $des^{+/-}$ (green). ALD error bars, ≥68% of scored embryos; solid lines, fits to Eq. 7; dashed lines, visual guidance marking saturating ALD, $S^{-/-}_{ALD}$, and critical treatment levels, $n_{c,\delta}$. **(B)** As in (A) but for MO. Concentration error bars, 2 SD. **(C)** Mean-field approximation, where each cell averages over the oscillation phases of all other cells, neglects amplitudes and spatial features of cyclic wave patterns. **(D)** Synchrony among cells, described by order parameter Z (top) or cyclic gene arrest pattern (bottom), decays over time with rate depending on treatment strength, n; below threshold Z_c, segment boundaries are defective, causing an ALD.

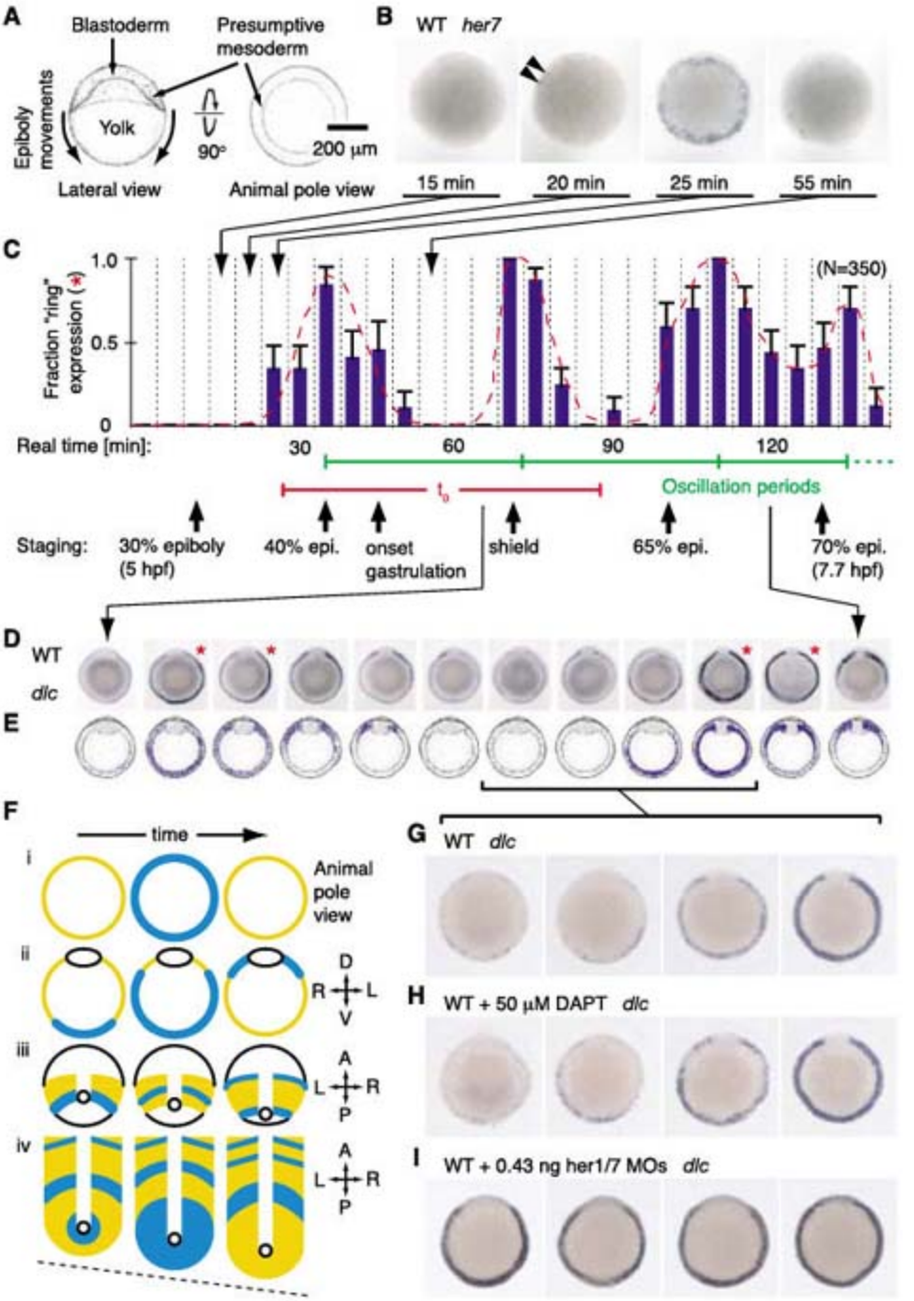

Fig. 3. The genetic oscillators of the segmentation clock are initiated synchronously in a Delta-Notch-independent manner. (**A**) Schematic of late zebrafish blastula stage immediately before mesoderm induction. (**B**) First detection (arrowheads) and first cycle of *her7* expression in presumptive mesoderm ring (animal pole view). (**C**) Temporal distribution of presomitogenesis cyclic gene oscillations; embryos scored for continuous "ring"-shaped expression [red asterisks in (D)] of *dlc* in early mesoderm. Red bar, estimated uncertainty for t_0 when desynchronization starts; error bars, 1 SEM. Red dashed line is for visual guidance. (**D**) *dlc* expression in representative embryos (vegetal view, dorsal to top). (**E**) Illustration of (D) with waves traveling around margin from ventral to dorsal. (**F**) Schematic of changes in cyclic gene expression patterns during different developmental stages: (i) cycle 1 during pregastrula, (ii) cycles 2 to 4 during early gastrula with dorsal side marked, (iii) cycles 5 and 6 during late epiboly with notochord primordium, and (iv) cycles 7 to 30+ during somitogenesis stages with tailbud. (**G** to **I**) Representative sibling embryos, laid over 20 min, showing oscillatory *dlc* expression after dimethyl sulfoxide (DMSO) carrier treatment (G) and DAPT treatment (H), but elevated, stable expression after MO targeting both *her1* and *her7* bHLH repressor protein mRNA (I).

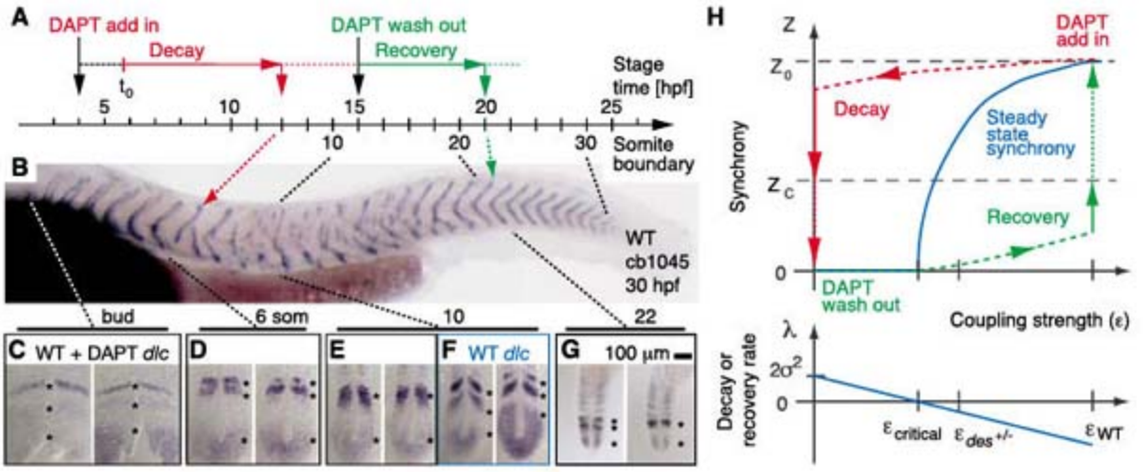

Fig. 4. Delta-Notch coupling is sufficient for self-organized resynchronization of the segmentation clock and rescue of morphological segmentation defects. (**A**) Timeline of DAPT pulse-chase experiment. (**B**) Six anterior segments formed correctly (S_{ALD} = 7), followed by ~15 disrupted segments (red bracket), followed by normally shaped segments posterior to 21st segment (S_{PLD} = 21). Control embryos in DMSO showed no defect phenotype (*14*); embryos remaining in DAPT showed no rescue (Fig. 1E). (**C** to **G**) Representative *dlc* PSM expression patterns, time points marked referring to (B). Two representative embryos showing transition from mildly affected cyclic expression stripes (C), degrading gradually (D) to typical salt-and-pepper pattern indicating desynchronization among cells (E) compared to expected WT pattern (F), and return of normal, symmetrical cyclic gene expression pattern (G). Asterisks mark *dlc* cyclic stripes [(C), (F), and (G)] or disordered expression domains [(D) and (E)]. (**H**) Schematic synchrony-coupling phase diagram (top) and decay or recovery rate-coupling dependency (bottom). Potential additional coupling pathways are neglected for simplicity (A = 0); axes not to scale.

existence of a synchronization transition in a population of biological genetic oscillators (*18*, *20*, *21*).

More generally, the analysis of other complex developing systems (*23*) would be amenable to the quantitative strategy used here. In particular, quantitative MO delivery can be interpreted as a tool to speed up mRNA decay with expected in vivo MO-mRNA binding rates of $K_b \sim 10^4\ M^{-1}\ s^{-1}$ (*13*). Consequently, molecular parameters can be estimated, such as the *notch1a* mRNA decay rate, $k_d \sim 0.1\ min^{-1}$ (*13*).

The onset of desynchronization (Fig. 1F) predicts the clock's initiation at or before $t_0 = 5.8 \pm 0.5$ hours. Around this developmental time point, the cells of the zebrafish presumptive mesoderm that will later become the somites are found in a marginal ring of the blastoderm; epiboly movements will subsequently draw the blastoderm over the yolk (Fig. 3A). We observed the earliest expression of cyclic genes *her1*, *her7*, and *dlc* at ~5.25 hours postfertilization (hpf): 10 min elapsed between first detection of scattered *her7*-positive nuclei and a subsequent ring of expression around the entire margin, which disappeared 30 min later, marking the first cycle of the segmentation clock (Fig. 3B and fig. S1) (*13*). Hence, the clock's initiation coincides with, or shortly precedes, the inferred onset of desynchronization, and initial synchrony among these genetic oscillators appears to be achieved by simultaneous gene induction.

Three more oscillatory cycles were found confined to the ring of the gastrulating mesoderm with an interval between maximum expression states of around 30 min, corresponding to the period of the segmentation clock (Fig. 3C). During these cycles, *dlc* expression started at the ventral side of the embryonic margin and moved dorsally, thereby forming a traveling wave (Fig. 3, D and E). Furthermore, period seemed to decrease, whereas cellular expression levels increased, which is characteristic for transients following bifurcation events (*18*). During the subsequent fifth cycle, a cyclic expression domain separated from the gastrula margin at 8.2 hpf and moved anteriorly. The earliest previously reported wave at 8.7 hpf (*15*, *24*, *25*) marked the sixth cycle and prefigured the first segment boundary. These five cycles before somitogenesis in zebrafish contrast to two observed in chick (*26*). Thus, throughout development, four related spatiotemporal oscillation patterns of the zebrafish's segmentation clock are now distinguishable (Fig. 3F).

To test the requirement of intercellular Delta-Notch signaling for clock initiation, we subjected WT embryos to DAPT. The oscillating expression patterns of *dlc* at 65% epibioly were indistinguishable from those of WT (Fig. 3, G and H). In contrast, embryos injected with MOs targeting the *h/E(Spl)* genes *her1* and *her7*, jointly required for segmentation along the entire axis (*15*, *27*), showed sustained *dlc* expression (Fig. 3I), indicating loss of cyclic gene oscillations. Thus, the first synchronous oscillations of the segmentation clock require h/E(Spl) transcriptional repressors, but, consistent with the desynchronization hypothesis (*5*), we found no evidence for a Delta-Notch requirement.

Although the clock attains initial synchrony via simultaneous initiation of its oscillators, according to Eqs. 2 and 3 a coupling-dependent, self-organized synchronization over multiple periods among initially unsynchronized oscillators (*18*, *20*, *21*) should also be possible. Embryos subjected to a DAPT pulse from 4 to 15 hpf (Fig. 4A) showed an ALD of $S_{ALD} = 6.1 \pm 1.1$ ($N = 9$) (Fig. 4B) and concomitant, profound loss of synchrony in cells of the tailbud and presomitic mesoderm (PSM) evidenced by a disordered *dlc* expression pattern (Fig. 4, C to F), equivalent to that in Delta-Notch mutants (*5*, *15*, *28*, *29*). After DAPT washout, normal segment formation and cyclic gene expression was recovered (Fig. 4, B to G). The position of the last defective segment defines a posterior limit of defects (PLD), which we estimated at $S_{PLD} = 23.2 \pm 2.1$ (~21 hpf), indicating a recovery time of ~10 oscillation periods. Thus, restoration of Notch coupling is sufficient for self-organized resynchronization (*18*, *20*, *21*) of these previously desynchronized genetic oscillators, whereby both decay and recovery processes can be represented as a trajectory in a synchrony-coupling phase diagram (Fig. 4H, top).

We have demonstrated two general mechanisms by which genetic oscillators can attain synchrony: (i) simultaneous induction and (ii) self-organized synchronization, which, in the case of the segmentation clock, were Notch-independent and Notch-dependent, respectively. Delta-Notch mutant zebrafish embryos would allow screening for compounds restoring Delta-Notch coupling (*30*), with potential therapeutic implications for human genetic mal-segmentation disorders (*31*). These Delta-Notch mutant phenotypes are now quantitatively understandable from the desynchronization hypothesis (*5*) in terms of the decay rate λ, that is, the difference in noise, $2\sigma^2$, and coupling strength, ε (Eq. 3 and Fig. 4H, bottom), which determines the segmentation defect position. From the lowest ALD observed (Eq. 6) and assuming alternative coupling pathways negligible ($A = 0$), we estimate the clock's noise of $2\sigma^2 \approx 0.8\ hour^{-1}$, consistent with our estimates of noise (*13*) stemming from cell movements (*5*) and genetic sources. The system's robustness R (Eq. 9) then gives the WT Notch coupling strength of $\varepsilon_{WT} = R \cdot 2\sigma^2 \approx 4\ hour^{-1}$. Thus, by using quantitative techniques for perturbation of gene function in combination with a physical theory of coupled phase oscillators, we were able to determine the essential dynamical properties that quantitatively account for a collective, morphological process in a complex developmental system.

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Materials and Methods
SOM Text
Figs. S1 to S3
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Rapid Emergence of Baculovirus Resistance in Codling Moth Due to Dominant, Sex-Linked Inheritance

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Insect-specific baculoviruses are increasingly used as biological control agents of lepidopteran pests in agriculture and forestry, and they have been previously regarded as robust to resistance development by the insects. However, in more than a dozen cases of field resistance of the codling moth *Cydia pomonella* to commercially applied *C. pomonella* granulovirus (CpGV) in German orchards, resistance ratios exceed 1000. The rapid emergence of resistance is facilitated by sex-linkage and concentration-dependent dominance of the major resistance gene and genetic uniformity of the virus. When the gene is fixed, resistance levels approach 100,000-fold. Our findings highlight the need for development of resistance management strategies for baculoviruses.

More than 2500 cases of insect resistance to chemical pesticides have been documented over the past 50 years (*1*, *2*). In contrast, baculoviruses have been used to control lepidopteran pests on 2 to 3 million hectares per year worldwide, with high specificity and low environmental impact and with only sporadic and anecdotal reports of resistance (*3*–*5*). Baculovirus virions are protected by a proteinaceous occlusion body (OB) that confers environmental stability and allows field application with conventional insecticide sprayers. Their narrow host range and high virulence make them one of the most selective pest control agents, widely used for the control of many agricultural and forestry pests including codling moth (*Cydia pomonella* L., Lepidoptera: Tortricidae) (*6*).

One of the most successful commercial baculovirus insecticides is the *C. pomonella* granulovirus (CpGV), now a cornerstone of codling moth control in both organic and integrated apple production. In many countries, CpGV products are among the very few control measures for this pest allowed in organic apple production. Without control, codling moth infestations can result in severe damage and complete loss of marketable fruits. In the last 3 years, enigmatic field observations in organic apple orchards in Germany and France suggested that CpGV was failing to control apple damage (*7*, *8*).

In 2003–06, we undertook a systematic survey of 13 organic orchards in southern Germany where the efficacy of CpGV had been reported as unsatisfactory. Concentration-mortality relations were determined in 14-day bioassays to estimate the median lethal concentrations (LC_{50}) of the commonly used Mexican isolate of

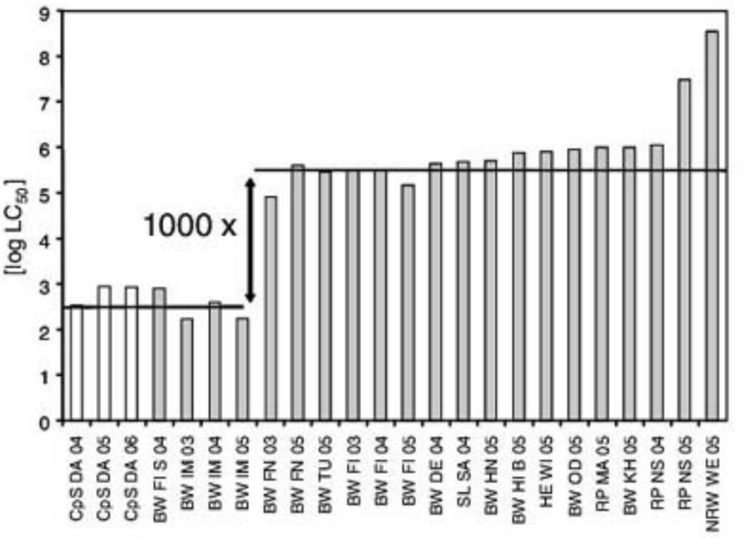

Fig. 1. CpGV susceptibility levels of codling moth populations from German orchards in 2003–05. The LC_{50}, in numbers of OBs per 1 ml of artificial diet, was estimated by probit analysis from 14-day mortality bioassays with neonate larvae. The resistance ratio is defined as the ratio of LC_{50} values of resistant and susceptible strains. Gray columns represent orchard-collected strains and white columns, the susceptible laboratory strain (CpS DA). The last two letters indicate the year of testing (CpS DA) or sampling (field populations). Laboratory-reared progeny from the field populations were tested the year after sampling.

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Table 1. Survivorship at day 7 and pupation at day 21 in crosses with CpGV-susceptible (CpS) and resistant (CpRR1) strains of codling moth, exposed to a discriminating concentration of 5.8×10^4 OB/ml as neonates. BC, back cross; f, female; m, male. Progeny genotypes are shown for two hypotheses: (Z), a single Z-linked resistance gene, or (A), a single autosomal resistance gene. R and S denote the resistant and susceptible alleles, respectively. F/n indicates the total number of families (F) and neonates (n) tested. [Exp (Z)] is the expected fraction of survivors, under the hypothesis of a single Z-linked resistance gene, with Z^R fully dominant to Z^S. [Exp (A)] is the expected fraction of survivors, under the hypothesis of a single autosomal resistance gene, with the degree of dominance of A^R estimated from the response of the F1a survivorship. At 21 days, "males" refers to the fraction of males among living pupae. The chi-square value applies to the goodness-of-fit test of the observed 7-day survivorships in the four backcrosses to the expected values under the Z-linkage (Z) or autosomal (A) hypothesis. *N.O., Sex ratio not observed because there were no living pupae at 21 days in this group.

Strain or cross	Progeny genotypes, by hypothesis		F/n	Fraction of survivors, day 7			Pupation, day 21	
	(Z)	(A)		Observed (SD)	Exp (Z)	Exp (A)	Pupated	Males
CpS	Z^SW, Z^SZ^S	A^SA^S	–/95	0.02 (N.O.)	0.00	0.02	0.00	(N.O.)*
CpRR1	Z^RW, Z^RZ^R	A^RA^R	10/251	1.00 (0.000)	1.00	1.00	0.97	0.56
F1a: CpSm × CpRR1f	Z^SW, Z^RZ^S	A^RA^S	10/394	0.57 (0.092)	0.50	0.57	0.09	1.00
BC1: F_1f × CpRR1m	Z^RW, Z^RZ^S	A^RA^S, A^RA^R	8/369	1.00 (0.008)	1.00	0.79	0.56	0.08
BC2: F_1m × CpRR1f	Z^SW, Z^RW, Z^RZ^S, Z^RZ^R	A^RA^S, A^RA^R	7/270	0.73 (0.103)	0.75	0.79	0.44	0.58
BC3: F_1f × CpSm	Z^SW, Z^SZ^S	A^SA^S, A^RA^S	10/458	0.00 (0.000)	0.00	0.30	0.00	(N.O.)*
BC4: F_1m × CpSf	Z^SW, Z^RW, Z^SZ^S, Z^RZ^S	A^SA^S, A^RA^S	7/308	0.47 (0.057)	0.50	0.30	0.25	0.09
χ^2, BC1-4					1.6	343.7		

CpGV (*9*, *10*). Compared with susceptible laboratory and field populations with LC_{50} values of ~170 to ~970 OB/ml of artificial diet, most field populations showed resistance ratios of ~1000, and two even exceeded 10,000-fold resistance levels (Fig. 1).

One of the resistant populations collected in 2003 (BW FI 03) was used to establish the CpR strain, which was reared in the laboratory without selection by virus. It maintained a stable ~100-fold resistance level over many generations, compared with the susceptible strain CpS. Mass crossing experiments between CpR and CpS had suggested an autosomal (i.e., not sex-linked), incompletely dominant inheritance of resistance (*11*). However, single-pair crosses between CpR and CpS yielded heterogeneous bioassay results, indicating that CpR still contained some susceptible individuals. To produce a genetically homogeneous strain for inheritance studies, offspring of single-pair CpR crossings (i.e., families) were screened with a discriminating CpGV concentration of 5.8×10^4 OB/ml. This concentration caused 95 to 98% mortality of CpS and <30% mortality (on average) of CpR in 7-day bioassays; however, single-pair CpR families showed a wide range of mortalities. Progeny from only those families with 0% mortality were selected and intercrossed in single pairs. After a second round of this screening process, progeny from the four single-pair families with 0% mortality were used to start the homogenized CpRR1 strain.

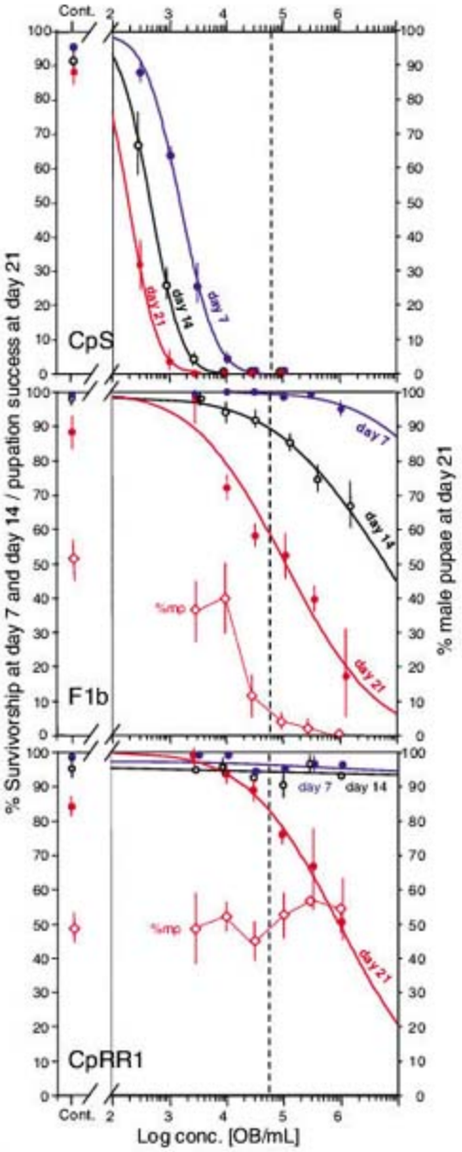

Fig. 2. Concentration-mortality responses of neonate codling moth larvae of CpS, CpRR1, and F1b (CpS females x CpRR1 males) exposed to different concentrations of CpGV. The survivorship of larvae (day 7, day 14) and the effect on pupal development (day 21) were analyzed using Probit analysis. The percentage of male pupae (%mp) was scored at day 21. On the left side of the graphs, the survivorships in the respective untreated controls (cont.) are given. The dashed line marks the discriminating virus concentration applied to neonates (see Table 1).

Inheritance of resistance in the CpRR1 strain was then investigated using single-pair crosses with CpS. When F_1 offspring of 10 single-pair crosses (F1a) between CpS males and CpRR1 females were tested at the discriminating concentration, 57% survived the 7-day bioassay (Table 1). These findings were consistent with the autosomal semidominant CpGV resistance previously reported for CpR (*11*), albeit at a higher resistance level. However, additional crosses combined with longer and more detailed bioassays led to a different conclusion. If resistance were determined by autosomal genes, then reciprocal single-pair backcrosses to the parental strains should yield similar results, independent of the sex of the F_1 parent. As shown in Table 1, this was not the case, and survivorship in the 7-day bioassay differed significantly from the hypothesis of autosomal inheritance ($\chi^2 = 343.7$, df = 4; $P < 0.0001$). In *C. pomonella* as well as most Lepidoptera, the sex chromosomes are ZZ in males and ZW in females (*12*). The bioassay data are consistent with a dominant resistance gene linked to the Z chromosome enabling 100% survivorship of either heterozygous Z^RZ^S or homozygous resistant Z^RZ^R males, as well as Z^RW females ($\chi^2 = 1.6$, df = 4; $P > 0.5$). Z^SZ^S males and Z^SW females would experience nearly 100% mortality in this bioassay, consistent with the behavior of CpS (Table 1).

The same bioassays were observed until day 21, when untreated control larvae and most of the treated CpRR1 would have pupated. By this time, some crosses had many surviving larvae that had stopped feeding but not yet pupated; these died a few days later, still in the larval stage. By using morphological and molecular methods, most of these nonpupating larvae were determined to be males. The pupation success and sex ratio (Table 1) were also consistent with a Z-linked resistance gene, with the additional property that most of the Z^RW females and homozygous Z^RZ^R males successfully pupated, whereas heterozygous Z^RZ^S males surviving day 7 subsequently died or failed to pupate and never became adults. Thus, with respect to adult fitness at the discriminating dose of 5.8×10^4 OB/ml, the Z^R allele is recessive, because males need two copies to survive to adulthood.

To explore the quantitative response of Z^RZ^S males to virus exposure, single-pair crosses (F1b) between CpS females and CpRR1 males were made, and bioassays were conducted at eight different virus concentrations. F1b progeny were expected to consist of only Z^RZ^S males and Z^RW females in equal proportions at hatching, thus differing from CpRR1 only in the presence of Z^RZ^S instead of Z^RZ^R males. Mortality was scored at days 7 and 14, and the fraction of treated individuals that had pupated was scored at day 21 (Fig. 2). CpS survivorship showed a strong virus concentration–mortality response, with LC_{50} values of 1425 and 501 OB/ml at days 7 and 14, respectively. CpRR1 survivorship was nearly 100% at all concentrations up to day 14, so the LC_{50} values could not be estimated. The LC_{50}-based resistance ratio of CpRR1 to CpS is likely to exceed 10^4 to 10^5. Further, a concentration-dependent decrease in successful pupation at day 21 was evident for CpRR1. The fraction of males among pupae fluctuated around 50%; thus, pupation success was dose-dependent but sex-independent in this strain. Mortality of F1b was very low by day 7, which confirmed the dominant action of Z^R in conferring early survivorship at virus concentrations that kill all Z^SZ^S males. The observed mortality on day 14 with increasing virus concentrations can be exclusively attributed to Z^RZ^S males, because Z^RW females survive all virus concentrations applied in the bioassays (compare CpRR1). Even more strikingly, the fraction of males among day 21 pupae decreased rapidly with increasing virus concentration as Z^RZ^S males died or remained living but did not pupate; rendering them effectively "genetically dead" as they did not develop to adulthood.

Thus, the surprisingly rapid emergence of CpGV resistance in orchard populations of codling moth can be explained by the interaction of three factors: sex-linkage, concentration-dependent dominance, and uniformity of the selective agent. First, the major resistance gene is Z-linked, and therefore, Z^RW females require only one copy of the resistance allele to survive virus exposure; this enables a faster initial selection response than the case of autosomally inherited resistance. Second, resistance measured as the probability of successful pupation after virus exposure in heterozygous Z^RZ^S males is dominant at low virus concentrations (further promoting a rapid initial selection response), but recessive at high virus concentrations. Hence, when Z^R occurs at a low frequency in an orchard population, we predict that it would be effectively selected for, even by low virus concentrations, both in Z^RW females and in Z^RZ^S males as a dominant gene. When the resistance allele frequency increases and virus applications are also increased by growers to compensate for control failures, the Z^RZ^R males enjoy an advantage over

Z^RZ^S males and Z^R would continue to increase in frequency, because it is selected for as a recessive in males. Third, all commercially available products in Europe contain the same CpGV isolate, which has high genetic homogeneity (*13*). Because organic apple growers rely heavily on CpGV and apply it repeatedly in each growing season, most of the organic orchards are continuously exposed to this virus isolate. Moreover, each OB of CpGV contains a single virion, in contrast to nucleopolyhedroviruses with up to several hundred virions per OB (*14*). The potential resistance-delaying effect of a mixture of virus genotypes in a single infection would thus be much weaker for CpGV.

The aim of insecticide-resistance management is to prevent or delay the selection of resistance by controlling the factors affecting allele frequencies in field populations. Our results make clear that this area of applied evolutionary biology is also highly relevant to the application of baculoviruses as biological control agents. Implementation of resistance monitoring and resistance management will be needed in order to sustain the ecological and economic benefits of this environmentally friendly class of biological insecticides.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/317/5846/1916/DC1
Methods and Materials
Tables S1 and S2
References

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Transcranial Magnetic Stimulation Elicits Coupled Neural and Hemodynamic Consequences

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Transcranial magnetic stimulation (TMS) is an increasingly common technique used to selectively modify neural processing. However, application of TMS is limited by uncertainty concerning its physiological effects. We applied TMS to the cat visual cortex and evaluated the neural and hemodynamic consequences. Short TMS pulse trains elicited initial activation (~1 minute) and prolonged suppression (5 to 10 minutes) of neural responses. Furthermore, TMS disrupted the temporal structure of activity by altering phase relationships between neural signals. Despite the complexity of this response, neural changes were faithfully reflected in hemodynamic signals; quantitative coupling was present over a range of stimulation parameters. These results demonstrate long-lasting neural responses to TMS and support the use of hemodynamic-based neuroimaging to effectively monitor these changes over time.

The study of brain function makes use of various techniques to modify neural processing. These include neurophysiological, surgical, and pharmacological approaches (*1*). In general, these techniques may be invasive, irreversible, and not confined to specific brain areas. In contrast, transcranial magnetic stimulation (TMS) (*2*) provides a noninvasive, reversible, and relatively localized approach that has substantial promise for basic neuroscience and clinical applications (*3*, *4*). In this technique, a magnetic coil placed above the scalp generates electric currents in the underlying cortex. As yet, the manner in which these currents affect neuronal processing is largely undetermined (*3*, *5*).

The full potential of TMS depends not only on a basic understanding of its neural effects, but also on the ability to make direct measurements of these changes in the human brain. This has recently been attempted by combining TMS with noninvasive brain-imaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) (*6*). These methods measure hemodynamics and metabolism to infer changes in neural activity based on known coupling between these variables (*7*). However, in certain conditions, neural activity may be uncoupled from local hemodynamics. For example, altered brain states such as seizures (*8*) and cortical spreading depression (*9*) result in complex and atypical physiological responses that do not fit standard models of neurovascular coupling. It is essential, therefore, to investigate both the direct neural effects of TMS and the relationships among neural, vascular, and metabolic parameters.

To provide an integrated view of the basic effects of TMS, we used several complementary techniques in a controlled physiological preparation. We applied short TMS pulse trains to the visual cortex of the anesthetized cat ($n = 8$) while simultaneously measuring tissue oxygen and neural activity (*10*–*12*). In separate experiments, we used 570-nm optical imaging of intrinsic signals to measure changes in total hemoglobin (Hbt) within the cortical vasculature (*12*–*14*). Each trial in our experimental paradigm (Fig. 1) included a pre-TMS baseline (40 s), a short TMS pulse train (1 to 4 s, 1 to 8 Hz), and a long recovery period (5 to 15 min). Throughout the trial, we alternated visual stimulation with a blank screen to assess the effects of TMS on both evoked and ongoing spontaneous activity (*12*). Elevation of spike rates during visual stimulation also permitted detection of signal decreases (*12*, *15*).

The neural effects of TMS application are shown in Fig. 2, A and B. An initial repeated-measures analysis of variance (ANOVA) on firing rate indicated significant main effects for activity state (spontaneous versus evoked, $F_{241,484} = 65.073$, $P < 10^{-13}$) and time (1 to 20 s after TMS, 30 to 90 s, or 180 to 210 s, $F_{241,484} = 3.473$, $P < 0.05$), as well as a significant interaction between these factors ($F_{241,484} = 9.931$, $P < 0.0001$) (*12*). Accordingly, post hoc tests (Wilcoxon signed-rank) revealed differential response time courses between activity states. Across the population, the spontaneous spike rate increased substantially (~200%) immediately after TMS (Fig. 2A, left) and remained elevated for ~60 s ($P < 0.001$; fig.

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S4A; fig. S5A, left). In contrast, the evoked firing rate (Fig. 2A, right) showed an immediate decrease (~50%) and remained significantly suppressed for more than 5 min ($P < 0.0001$; fig. S4B; fig. S5A, middle). Analogous changes occurred in the power of local field potentials (LFPs) (Fig. 2B), although a distinction was evident with regard to frequency band (fig. S5B). Spontaneous LFP power at higher frequencies (>40 Hz) showed immediate enhancement, whereas lower frequencies (<40 Hz) exhibited a prolonged reduction, similar to evoked activity. This distinction is likely related to the different physiological processes reflected by these frequency ranges (*12*, *16*).

To determine how neural changes are reflected in metabolic and vascular signals, we examined measurements of tissue oxygen colocalized with the neural recordings. A repeated-measures ANOVA showed a significant main effect for time ($F_{111,224} = 56.609$, $P < 10^{-16}$) but no effect for activity state ($F_{111,224} = 0.0001$, $P > 0.98$; fig. S6B). Therefore, oxygen was further analyzed as a single continuous variable (*12*, *17*). Post hoc Wilcoxon signed-rank tests revealed a biphasic response pattern for oxygen (Fig. 2C). An immediate increase peaked at 10 to 15 s after TMS (Fig. 2C, inset; $P < 0.001$) and was followed by an extended reduction lasting over 2 min ($P < 0.01$). Separate measurements of Hbt (Fig. 2D) revealed a similar response: a peak at 10 s (Fig. 2D, inset; $P < 10^{-7}$) and a subsequent prolonged decrease (over 1 min, $P < 0.001$). This independent data set confirms that changes in blood flow underlie a substantial component of the oxygen response.

The above ANOVAs also revealed significant main effects of pulse frequency (1, 4, or 8 Hz) on neural ($F_{241,484} = 3.522$, $P < 0.05$) and oxygen ($F_{111,224} = 5.739$, $P < 0.005$) data. This raises the possibility that neural and hemodynamic response components covary with stimulation parameters. During the initial response component (<20 s), an increase in TMS pulse frequency caused a monotonic increase in the amplitude of the early oxygen peak and the level of spontaneous neural firing (Fig. 3A, upper right quadrant). At later time points (30 to 90 s), reductions in both tissue oxygen and evoked spiking were larger with

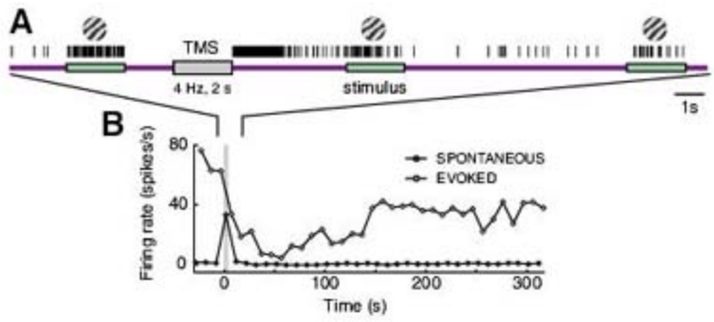

Fig. 1. TMS and visual stimulation paradigm. **(A)** Timeline of a sample trial showing stimulus presentations (green) and interstimulus intervals (ISIs) (purple). The visual stimulus was a high-contrast grating displayed for 2 s at intervals of 8 s. TMS (gray box) was applied during an ISI. TMS pulse trains were varied in frequency and duration on separate trials. Single-unit spikes (black ticks), LFP (not shown), and tissue oxygen (not shown) were recorded continuously; activity during TMS was not analyzed because of artifact contamination (fig. S3A). **(B)** The full TMS trial. Evoked activity represents neural responses during stimulus presentations, and spontaneous activity represents responses that occurred during ISIs.

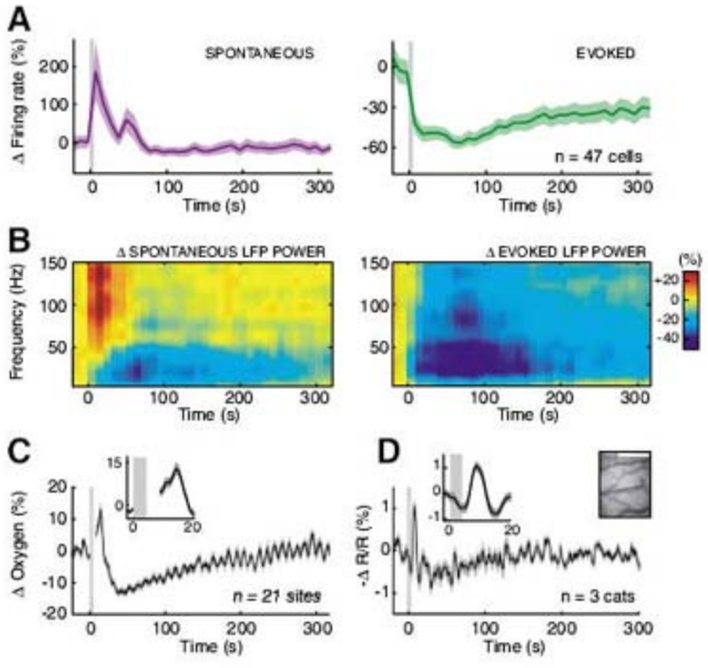

Fig. 2. Effects of TMS on neural, oxygen, and optical imaging signals. Shown are average time courses of **(A)** spiking activity, **(B)** LFP power, **(C)** tissue oxygen, and **(D)** total hemoglobin (Hbt) before and after TMS (gray box). All signals are expressed as a percent change from their pre-TMS baselines. Shaded areas represent ±1 SEM. (A) Spontaneous (left) and evoked (right) spiking activity ($n = 47$ cells). (B) Spontaneous (left) and evoked (right) LFP power ($n = 42$ sites). (C) Tissue oxygen ($n = 21$ sites). (D) Hbt ($n = 3$ animals). Insets in (C) and (D) show initial increases. Time periods containing TMS artifacts were removed (fig. S3B). In (D), Hbt was measured by recording the change in 570-nm light reflectance (ΔR/R) from the cortical surface (upper right); scale bar, 1 mm.

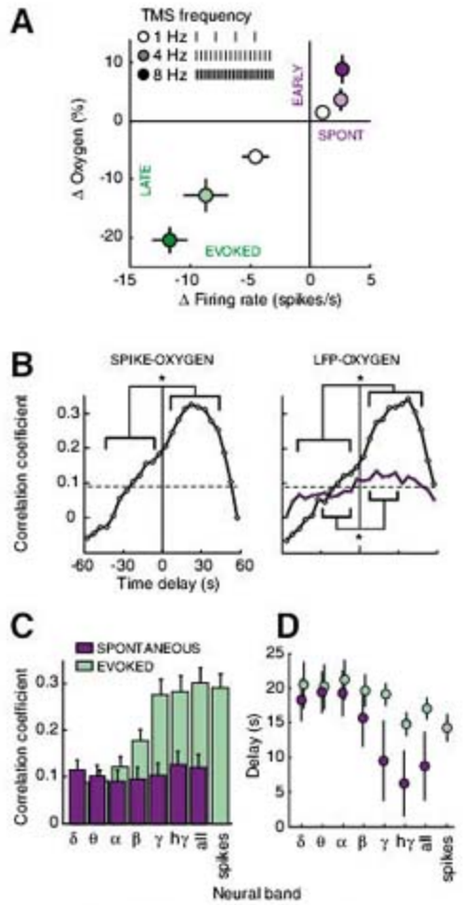

Fig. 3. Covariation between neural and oxygen data. **(A)** Changes in spiking activity and oxygen as a function of TMS pulse frequency. Neural activity was indexed by spontaneous spiking during the initial phase (0 to 20 s after TMS) and by evoked spiking during the later phase (30 to 90 s) (*15*). Error bars in this and subsequent panels represent ±1 SEM; where error bars are not visible, the error was smaller than the plot symbol. **(B)** Time-lag correlation between oxygen and neural signals (left: spiking activity, $n = 117$ trials; right: LFP power, 1 to 150 Hz, $n = 77$ trials). Positive time lags indicate a shift of the neural signal forward in time relative to the oxygen signal. Neural-oxygen correlations were performed for evoked spiking and LFP activity (green) and for spontaneous LFP signals (purple); a similar analysis with spontaneous spiking could not be performed because of low baseline firing rates. Correlation coefficients above the dashed lines are significant over the population ($P < 0.05$, t test). Asterisks denote correlations at positive time lags that are significantly greater than those at negative delays ($P < 0.05$, paired t test). **(C)** Neural-oxygen correlation magnitude across bands. LFP bands are defined as follows: δ (delta; 1 to 4 Hz), θ (theta; 4 to 8 Hz), α (alpha; 8 to 12 Hz), β (beta; 12 to 20 Hz), γ (gamma; 20 to 80 Hz), hγ (high-gamma; 80 to 150 Hz), all (1 to 150 Hz). **(D)** Neural-oxygen correlation latencies across bands.

higher pulse frequencies (Fig. 3A, lower left quadrant). A more limited data set for pulse train duration showed an analogous trend (fig. S7B). These data suggest that the physiological effects of TMS increase in a dose-dependent manner within this regime of TMS application.

The relationship between decreases in oxygen and neural activity is consistent with recent studies of negative hemodynamic responses (*18*, *19*). However, reductions in oxygen may be a cause of neural suppression rather than a consequence. In this scenario, normal neural function would be limited by hypoxic conditions (*12*). To investigate this possibility, we performed a time-lag correlation analysis of simultaneously acquired neural and oxygen data (fig. S8). Both spike rate (Fig. 3B, left) and LFP power (Fig. 3B, right) showed significant correlations with oxygen across a broad range of time lags ($P < 0.05$, t test). Notably, correlation coefficients were significantly greater at time lags in which the neural signal was shifted forward in time ($P < 0.05$, paired t test). Furthermore, LFP-oxygen correlations were band-specific with regard to magnitude and latency. Gamma and high-gamma bands exhibited the strongest correlations (Fig. 3C), as reported in previous studies of hemodynamic coupling (*20*). Higher-frequency bands also exhibited peak correlations at shorter latencies (Fig. 3D). This trend, which was most pronounced for spontaneous activity, resulted from initial response increases present in higher-frequency but not lower-frequency bands (Fig. 2B, left). These analyses, along with additional experiments (fig. S9) (*12*), suggest that oxygen responses follow neural activity in a manner consistent with neurovascular coupling (*21*–*24*).

A striking aspect of our data is the long duration of neural and hemodynamic changes given the short application of TMS. Although most human studies using similar stimulation paradigms have demonstrated short-term effects, several studies have noted changes in cortical excitability on the order of minutes (*25*, *26*). Human studies using longer-duration stimulation have shown effects lasting hours or even days (*27*, *28*). Such long-term changes in neural function are thought to develop via spike timing–dependent plasticity (*27*, *29*, *30*). Notably, alterations in synaptic efficacy have been linked to changes in the temporal relationship between spikes and LFP oscillations (*31*, *32*). To examine our data for a link between spike timing and long-term neural changes, we performed an additional analysis of phase relationships between single-unit spikes and LFP oscillations (*12*, *33*). For pre- and post-TMS time windows, we quantified the degree of phase locking from the distribution of LFP phases at which spikes occurred (Fig. 4A). A striking example of TMS-induced changes in phase distributions is shown for spontaneous activity in Fig. 4B. Compared to the pre-TMS baseline (blue), spike timing relative to the theta oscillation was strongly desynchronized, as evidenced by the increased spread of the distribution after TMS (red). Across all frequency bands, spontaneous activity showed significant reductions in phase locking within the first 30 s after TMS (Fig. 4C, left, $P < 0.05$, randomization test). By 90 s, this index approached baseline values, and in the gamma band it actually exhibited a significant increase ($P < 0.05$). Somewhat similar effects were present in evoked activity (Fig. 4C, right). Phase locking to oscillations in the delta band were strongly reduced, whereas increases were present in both the gamma and high-gamma bands ($P < 0.05$). The capacity of TMS to disrupt precise timing of signals between interconnected neurons advocates its ability to alter brain plasticity (*27*, *29*, *30*) in a number of neuropsychiatric contexts (*4*).

Consistent with previous work (*29*, *34*, *35*), our results reveal long-lasting neural and hemodynamic consequences of TMS that covary with stimulation duration and frequency. In contrast, other studies have reported a distinction whereby low-frequency stimulation (≤1 Hz) causes suppression and high-frequency stimulation (≥8 Hz) leads to facilitation (*5*). However, this division appears to be oversimplified (*5*, *36*). The precise effects of brain stimulation are fundamentally dependent on many factors (*37*). For example, several groups have found that identical TMS paradigms elicit opposite physiological effects when applied to neighboring cortical regions (*34*, *38*) or different subjects (*36*). Within a single site, TMS can produce differential effects depending on the activity state to which stimulation is paired (*36*, *39*). Such reports of variability and state-dependence reveal the complex action of TMS, yet also hint at its potential flexibility as an interventional technique.

Harnessing this potential requires the ability to measure the precise neural effects of TMS over different brain regions and time intervals. Our findings show that TMS-induced modifications of neural activity are readily observed in cerebral hemodynamics, which can be detected by standard neuroimaging techniques. This result confirms recent combined TMS-fMRI studies in which correlations were reported between TMS-induced behavioral changes and hemodynamic signals in functionally related brain regions (*39*, *40*). The capacity of brain imaging to monitor the temporal progression of physiological changes induced by TMS may prove highly beneficial for the development and optimization of both basic neuroscience and clinical applications.

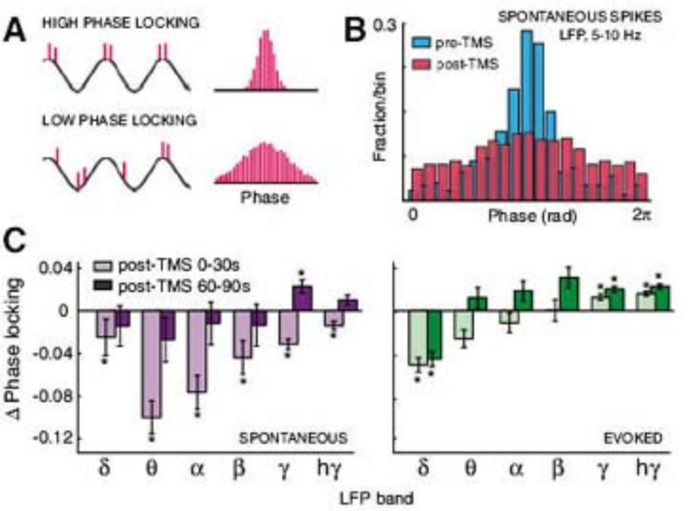

Fig. 4. Effects of TMS on spike timing relative to LFP oscillations. **(A)** Illustration of phase locking between spikes (red) and LFP (black). During periods of high phase locking (top), spikes occur at consistent phases in the LFP (left), and the resulting phase distribution is narrow (right). **(B)** Example of a TMS-induced change in phase locking. Before TMS (blue), spontaneous spikes occur more frequently at preferred phases of theta-band oscillation. In the first 30 s after TMS (red), the phase distribution broadens, indicating a decrease in phase locking. **(C)** Changes in phase locking across LFP frequency bands for spontaneous (left) and evoked (right) activity. Change in phase locking was determined by comparing the vector strengths (one minus the circular variance) of phase distributions before and after TMS. Light bars show changes in the first 30 s after TMS; dark bars show changes at 60 to 90 s. Asterisks indicate significance ($P < 0.05$, randomization test).

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Supporting Online Material
www.sciencemag.org/cgi/content/full/317/5846/1918/DC1
Materials and Methods
Figs. S1 to S9
References

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Genomic Minimalism in the Early Diverging Intestinal Parasite *Giardia lamblia*

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The genome of the eukaryotic protist *Giardia lamblia*, an important human intestinal parasite, is compact in structure and content, contains few introns or mitochondrial relics, and has simplified machinery for DNA replication, transcription, RNA processing, and most metabolic pathways. Protein kinases comprise the single largest protein class and reflect *Giardia*'s requirement for a complex signal transduction network for coordinating differentiation. Lateral gene transfer from bacterial and archaeal donors has shaped *Giardia*'s genome, and previously unknown gene families, for example, cysteine-rich structural proteins, have been discovered. Unexpectedly, the genome shows little evidence of heterozygosity, supporting recent speculations that this organism is sexual. This genome sequence will not only be valuable for investigating the evolution of eukaryotes, but will also be applied to the search for new therapeutics for this parasite.

Giardia lamblia (syn. *G. intestinalis*, *G. duodenalis*) is the most prevalent parasitic protist in the United States, where its incidence may be as high as 0.7% (*1*). Worldwide, giardiasis is common among people with poor fecal-oral hygiene, and major modes of transmission include contaminated water supplies or sexual activity. Flagellated giardial trophozoites attach to epithelial cells of the small intestine, where they can cause disease without triggering a pronounced inflammatory response. There are no known virulence factors or toxins, and variable expression of surface proteins may allow evasion of host immune responses and adaptation to different host environments. Trophozoites can differentiate into infectious cysts that are transmitted through feces.

Unusual features of this enigmatic protist include the presence of two similar, transcriptionally active diploid nuclei and the absence of mitochondria and peroxisomes. *Giardia* is a member of the Diplomonadida, which includes both free-living (e.g., *Trepomonas*) and parasitic species. The phylogenetic position of diplomonads and related excavate taxa is perplexing. Ribosomal RNA (rRNA), vacuolar ATPase (adenosine triphosphatase), and elongation factor phylogenies identify *Giardia* as a basal eukaryote (*2*–*4*). Other gene trees position diplomonads as one of many eukaryotic lineages that diverged nearly simultaneously with the opisthokonts and plants. Discoveries of a mitochondrial-like *cpn60* gene and a mitosome imply that the absence of respiring mitochondria in *Giardia* may reflect adaptation to a microaerophilic life-style rather than divergence before the endosymbiosis of the mitochondrial ancestor (*5*, *6*). Because of its impact on human disease and its relevance to understanding the evolution of eukaryotes, we embarked upon a genome analysis of *G. lamblia*.

The genome of *G. lamblia* WB clone C6 (ATCC50803) is ~11.7 MB in size, distributed on five chromosomes. The edited draft genome sequence contains 306 contigs on 92 scaffolds (Supporting Online Material). The genome is compact. We identified 6470 open reading frames (ORFs) with a mean intergenic distance of 372 base pairs (bp) (Table 1). Approximately 77% of the assembled sequence defines ORFs, of which 1800 overlap and 1500 more are within 100 nucleotides (nt) of an adjacent ORF. Serial analysis of gene expression (SAGE) and cDNA sequences provided transcriptional evidence for 4787 of these ORFs (Supporting Online Material).

Although the total number of ORFs is similar to that of yeast, many specific giardial pathways appear simple in comparison with those of other eukaryotic organisms. *Giardia*'s genome encodes a simplified form of many cellular processes: fewer and more basic subunits, incorporation of single-domain bacterial- and archaeal-like en-

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zymes, and a limited metabolic repertoire commonly observed in parasites. We did not detect these missing components in searches of assembled and unassembled reads; however, they may be highly divergent and difficult to recognize. Others may be nonessential or functionally redundant with other proteins in the same or another pathway. The host may provide essential metabolic products for an incomplete pathway, but this is a highly improbable explanation for missing structural proteins or subunits of core machinery.

DNA synthesis, transcription, RNA processing, and cell cycle machinery are simple (Fig. 1). The occurrence of only two origin recognition complex proteins (Orc4 and Orc1/Cdc6) in *Giardia* and the absence of regulatory initiation proteins (e.g., Cdt1, Dpb11, Cdc45, MCM10, and Gemini) are comparable to Archaea. *Giardia* has three replicative B-type DNA polymerases (Polα, Polδ, and Polε). The occurrence of four subunits in *Giardia*'s Polα/primase complex is typical of other eukaryotes, whereas the compositions of Polε and Polδ resemble the corresponding polymerases in Archaea. Most giardial DNA polymerase accessory proteins are typically eukaryotic.

Relative to *Saccharomyces*, *Giardia* has retained most of the RNA polymerase I (RNAPI), RNAPII, and RNAPIII core peptides. Seven proteins are missing, but six of these are unique subunits that occur in only one RNAP (*7*). Moreover, *Giardia* contains only 4 of the 12 transcription initiation factors present in *Saccharomyces*. The absence of polymerase core peptides is unlikely to be due to our failure to recognize highly diverged homologs in *Giardia*, because the missing proteins represented RNAP-specific elements rather than a random sampling of both shared and unique RNAP subunits. Absence of homologs to many of the unique subunits required for transcription is consistent with an evolutionary model hypothesizing that

Table 1. Comparison of eukaryotic genome content and organization.

	Saccharomyces cerevisiae	*Plasmodium falciparum*	*Trypanosoma brucei*	*Leishmania major*	*Entamoeba histolytica*	*Encephalitozoon cuniculi*	*Trichomonas vaginalis*	*Giardia lamblia*
Size (MB)	12.5	22.8	26.1	32.8	~24	2.3	~160	**11.7**
%G+C content	38.3	19.4	46.4	59.7	~25%	47.6	32.7	**49.0**
Proteins encoded	5770	5268	9068	8272	9938	1997	25,949	**6470**
Mean CDS (bp)	1424	2283	1592	1901	1170	1077	929	**1283**
Mean intergenic distance (bp)	515	1694	1279	2045	1245	129	1165	**372**
Gene density, per kbp	0.48	0.23	0.32	0.25	0.41	0.97	0.34	**0.58**
Introns	272	7406	1	0	~2500 predicted	2	65	**4**
tRNAs	275	44	65	83	Subtelomeric arrays	44	479	**63**

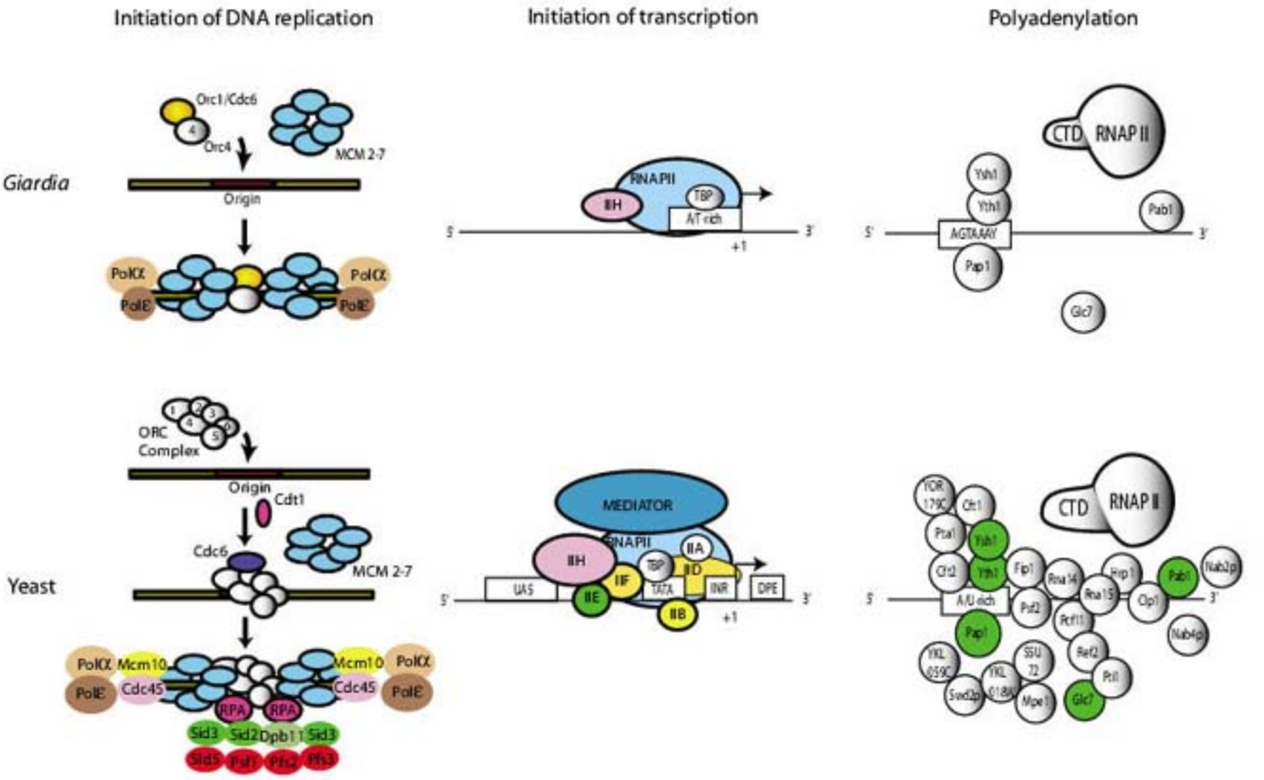

Fig. 1. Comparison of selected multiprotein complexes between *Giardia* and the yeast *Saccharomyces cerevisiae*. Initiation of replication: Multiple initiator proteins assemble at the origins of replication in *S. cerevisiae* during the cell cycle. *Giardia* has fewer origin recognition proteins (Orc) and most of the initiators of the pre-initiator complex. Initiation of transcription: Transcription in *S. cerevisiae* is initiated by the pre-initiation complex (PIC) consisting of the RNAPII core complex (12 subunits) and general transcription factors containing several subunits: TFIIA (2), TFIIB (1), TFIID (TBP plus14 TAFs), TFIIF (3), TFIIE (2), TFIIH (10), and the Mediator (24). These factors recognize DNA elements in the promoter, including the upstream activating sequence (UAS), the TATA box, the initiator element (INR), and the downstream promoter element (DPE). *Giardia* promoters have an AT-rich initiator element and lack many of the general transcription factors. Polyadenylation: The polyadenylation complex in *S. cerevisiae* recognizes an A/U-rich sequence, and it contains at least 25 proteins and the largest subunit of RNAPII with its C-terminal domain (CTD). The preferred polyadenylation signal in *Giardia* is AGTAAY, and *Giardia* has very few of the yeast polyadenylation proteins and a diverged CTD. Yth1 corresponds to CPSF30 and Ysh1 corresponds to CPSF73 in mammals.

class-specific polymerase subunits arose after the divergence of diplomonads.

A single intron with a noncanonical 5′ splice site was identified in a 2Fe-2S ferredoxin gene, along with components of the spliceosome (*8*). We generated trophozoite cDNAs and examined alignments of conserved proteins to identify other possible introns. We found three candidates, in genes for ribosomal protein L7A, a dynein light-chain protein, and an unknown protein. Two were confirmed by reverse transcription–polymerase chain reaction, and the RPL7A intron was independently reported (*9*). These new candidates show canonical GT/AG splice sites and contain an AC-repeat motif, [AC]CT[GA]AC[AC]CACAG (fig. S1). The AC-repeat motif is very like that common to *Trichomonas* introns [ACTAACACACAG (*10*)], suggesting a shared splicing mechanism. An intron has also been reported in the excavate *Carpediomonas* (*11*).

Giardia's machinery for RNA processing is less complex than that of other eukaryotes, but the presumed polyadenylation signal (AGUAAA) (*12*) resembles that of other eukaryotes (AAUAAA). Searches for *Giardia* sequences that are similar to the many polyadenylation factors in yeast and other eukaryotes identified relatively few homologs (Fig. 1). *Giardia* has a relative paucity of enzymes for posttranslational modification. Like *Plasmodium*, it lacks the vast majority of genes encoding glycosyltransferases and so makes the shortest N-glycan precursor yet identified, dolichol-PP-$GlcNAc_2$ (*13*). *Giardia*, like *Trypanosoma* and Archaea, has a single-subunit oligosaccharyltransferase for transferring N-glycans from the lipid precursor to the peptide (*14*), compared with eight in yeast and humans. Unlike most eukaryotes, *Giardia* has an N-glycan–independent quality-control system for protein folding (e.g., chaperones, protein disulfide isomerases, and peptidyl-prolyl cis-trans isomerases) and protein degradation. *Giardia* has fewer nucleotide sugar transporters than any other eukaryotic genome, including just one for uridine 5′-diphosphate (UDP)–GlcNAc (*15*). *Giardia* is missing the set of glycosyltransferases that typically modify N- and O-linked glycans in the Golgi lumen. Instead, *Giardia* has a cytosolic glycosyltransferase, rare among protists, which adds O-linked GlcNAc to Ser and Thr of cytosolic proteins (*15*).

Giardia has a conventional endoplasmic reticulum (ER) with conserved chaperones (BiP, Hsp90, DnaJ), but is unusual in having five protein disulfide isomerases, each with only a single active site (*16*), and in lacking the Ero1 protein that drives disulfide formation in the ER lumen. Membrane transport in *Giardia* is unlike that of other parasitic protozoa (*17*, *18*). Despite the highly polarized cell structure, there is no conclusive evidence for a stacked Golgi apparatus or cisternae for posttranslational maturation of secretory cargo except in encysting trophozoites. Only a few Rabs, SNAREs (soluble *N*-ethylmaleimide–sensitive factor attachment protein receptors), and a small number of adaptor protein (AP) complexes participate in vesicle docking and membrane fusion. Unlike all other eukaryotes that have at least three AP complexes, *Giardia* encodes only two. The presence of only two APs with no indication of pseudogenes or orphan subunits argues for a simple membrane transport system in *Giardia*.

Two rounds of cytokinesis, accompanied by a single round of nuclear division, occur during excystation. *Giardia*'s transcriptionally equivalent nuclei must synchronously divide in trophozoites and form quadrinucleate, 16N cysts (*19*). The presence of homologs to yeast Cin8, polo kinase, *aurora* kinase, and antiparallel microtubule bundling proteins suggests that the necessary spindle apparatus machinery is present. We identified giardial homologs of several mitotic exit network (MEN) proteins, indicating that regulation of cytokinesis in *Giardia* may be similar to that of yeast in which MEN coordinates nuclear division with cytokinesis. Homologs of actin, cyclin-dependent kinases, and the mitotic cyclins A and B are present in *Giardia*. However, the lack of myosin indicates that the actin-myosin cleavage furrow previously found in all eukaryotes is not present in *Giardia*. Possibly a nonmyosin, adhesion-dependent cytokinesis mechanism exists in *Giardia*, as in some mutants of *Dictyostelium* (*20*).

Like many other microaerophilic eukaryotic parasites, *Giardia* exhibits a limited metabolic repertoire. There are essentially no homologs for enzymes in the Krebs cycle and, except for well-known scavenging pathways, no evidence of vestigial genes associated with purine and pyrimidine biosynthesis. Amino acid metabolism is even more limited, although all tRNA synthetases are present. For lipid metabolism, the *Giardia* genome contains enzymes capable of limited fatty acid extension and sphingomyelin assembly, as well as phospholipid headgroup exchange and modification. Although not sufficient for de novo synthesis of lipids, these enzymes allow for remodeling of membrane components.

Glycolytic activities associated with enzymes involved in hexose processing and the interconversion and phosphorylation to fructose-1,6-phosphate glycolysis are more similar to bacterial than to higher eukaryal homologs (Fig. 2) (*21*). Some of these bacterial-like proteins share similarity with genes in *Entamoeba* and *Trichomonas* (table S3). Yet, the predicted origins of the sequences appear to be independent of each other and are not associated with a particular bacterial group.

Giardia metabolizes arginine by the anaerobic arginine dihydrolase pathway (Fig. 2), originally described in bacteria but unknown in eukaryotes other than *Trichomonas* (*22*). Arginine deiminase, ornithine carbamoyltransferase, and carbamate kinase generate ammonia, ornithine, and adenosine 5′-triphosphate (ATP), and all three archaeal-like enzymes are highly expressed. Trophozoites thus deprive host intestinal epithelial cells of arginine for nitric oxide biosynthesis and thereby dampen innate defenses (*23*, *24*). During encystation, *Giardia* synthesizes UDPGalNAc from fructose-6-phosphate by an unusual, five-enzyme bacterial-like pathway (Fig. 2). Many eukaryotes use the first enzyme, glucosamine-6-phosphate isomerase, to generate glucosamine-6-phosphate from fructose-6-phosphate and ammonia for glycolysis. Instead, *Giardia* uses ammonia from arginine metabolism to drive the synthesis of glucosamine-6-phosphate for cyst wall polysaccharide biosynthesis. Although *Giardia* is microaerophilic and consumes oxygen, it lacks the conventional enzymes superoxide dismutase and catalase for detoxifying reactive oxygen species (*25*).

Motility and attachment to host cells are essential for the parasitic life-style of *Giardia*. The microtubule cytoskeleton organizes *Giardia*'s eight basal bodies and flagella, as well as other structures unique to the genus, including the ventral disk and median body (table S4). The giardial cytoskeleton undergoes dramatic changes throughout the life cycle. General signaling proteins (protein kinase A, Erk kinase, calmodulin) and a protein phosphatase localize to the basal bodies, paraflagellar dense rods, and disk. The basal bodies may act as a control center that coordinates the other cytoskeletal structures during growth and differentiation. The microtubule system is well conserved and includes all five tubulin forms, proteins involved in microtubule modification, organization, and assembly (centrins, tubulin-specific chaperones, tubulin tyrosine ligase). There are coding regions for microtubule motor proteins, including kinesins and 12 dynein heavy chains.

The most notable departure from conserved cytoskeletal structure is the absence of cytoplasmic dynein and the divergent nature of the microfilament cytoskeleton. The genome contains a single actin gene, yet does not encode other classical microfilament proteins. On the basis of sequence similarities, the three genes encoding actin-related proteins participate in chromatin remodeling, rather than cytoskeletal structure. The absence of classic microfilament-associated proteins extends to actin modification, organization, and assembly proteins. In contrast to studies that used heterologous antibodies (*26*, *27*), permissive searches of the *Giardia* genome failed to identify actin-associated proteins, myosins, or any members of the microfilament-specific motor protein family (*28*). *Trichomonas*, which may be a sister lineage, also lacks myosin. Either novel, divergent proteins substitute functionally for the missing proteins or altered cytoskeletal dynamics accommodate their absence. *Giardia* contains several unusual cytoskeletal protein families including α-giardins (annexin homologs), β-giardins (striated fiber assemblin homologs), the GASP-180 family (*29*), and several microtubule-associated coiled-coil proteins.

Giardia has 276 putative protein kinases (fig. S2) including members from 43 of the 61

primordial kinase subfamilies present in widely diverged eukaryotes (ciliates, fungi/metazoa, plants, *Dictyostelium*). *Trichomonas* also has a greatly expanded kinome, which might reflect their putative sister relationship or commonalities in the parasitic life-style. *Giardia* has no tyrosine-specific or histidine kinases. Most notable is that 180 (~70%) of the putative giardial protein kinases belong to the NIMA (Never in Mitosis Gene A)–Related Kinase (NEK) family, and that 137 of them are predicted to be catalytically inactive. By contrast, most organisms have fewer than 10 NEK kinases.

This non-NEK kinome is the most compact known from any eukaryote, and so it is of specific functional and evolutionary interest in defining the minimal eukaryotic kinome. Broad-spectrum signal transduction proteins gain specificity by localization to specific cellular target structures. *Entamoeba histolytica*, another intestinal protozoan parasite, has >80 putative transmembrane kinases (*30*), but in stark contrast, only four predicted giardial kinases have transmembrane domains. Giardial kinases may have other means of targeting; many have either ankyrin repeats (*29*), coiled-coiled domains, or both, which may allow for specific localization within the cell. Protein dephosphorylation is also critical in signal transduction networks. *Giardia* has ~32 predicted protein phosphatases, but only one is predicted to be membrane associated.

Giardial protein sequences commonly show insertions of amino acids when compared to their

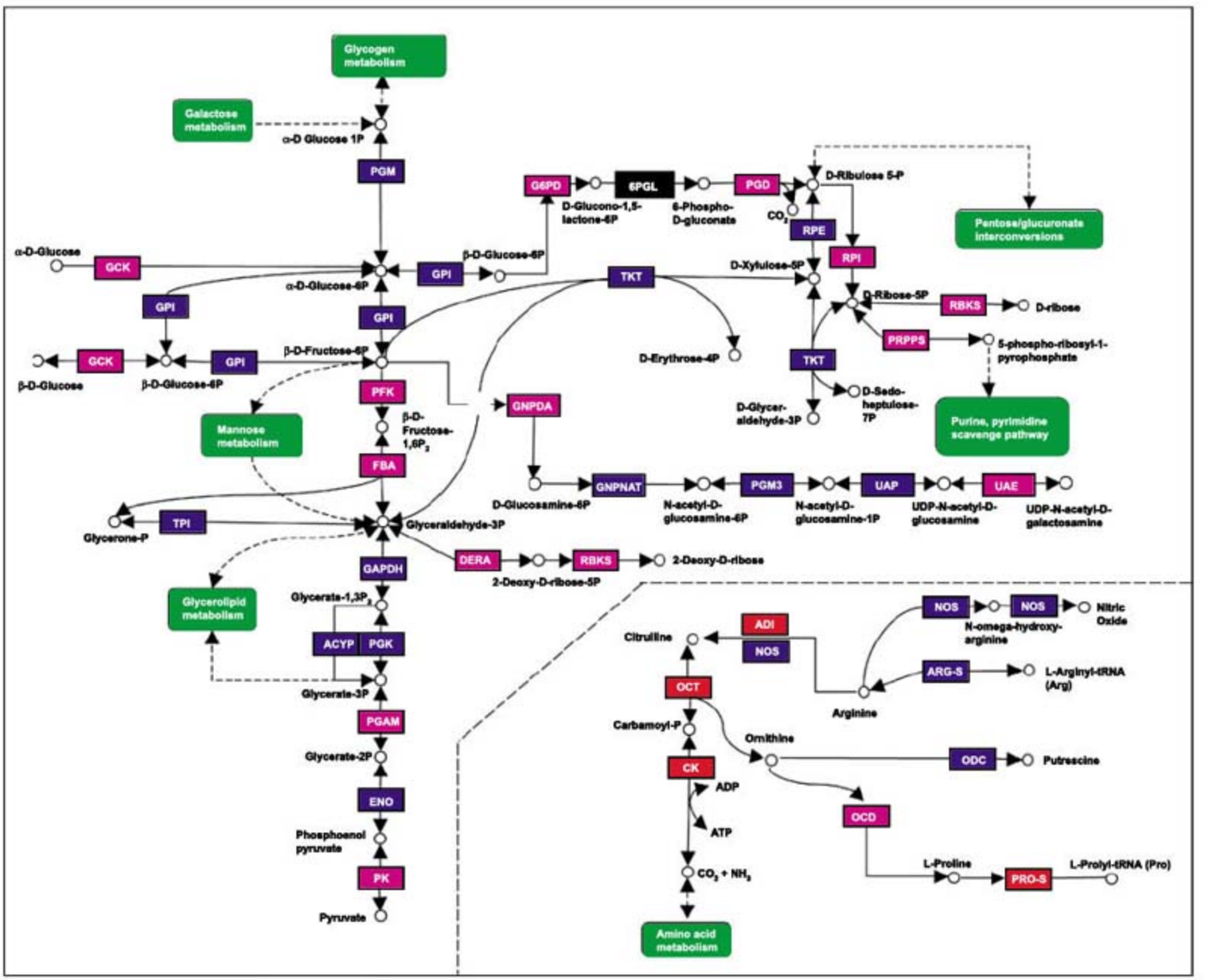

Fig. 2. Glucose, pentose-phosphate, and arginine metabolism in *Giardia*. Color coding denotes similarity to archaeal homolog (red), bacterial homolog (purple), or eukaryal homolog (blue). Black indicates that no homolog was found. Abbreviations and Enzyme Commission numbers: 6PGL, 6-phosphogluconolactonase, 3.1.1.31; ACYP, acylyphosphatase, 3.6.1.7; ADI, arginine deiminase, 3.5.3.6; ARG-S, arginyl-tRNA synthetase, 6.1.1.19; CK, carbamate kinase, 2.7.2.2; DERA, deoxyribose-phosphate aldolase, 4.1.2.4; ENO, enolase, 4.2.1.11; FBA, fructose-bisphosphate aldolase, 4.1.2.13; G6PD, glucose-6-phosphate dehydrogenase, 1.1.1.49; GAPDH, glyceraldehyde-3-phosphate dehydrogenase, 1.2.1.12; GCK, glucokinase, 2.7.1.2; GNPDA, glucosamine-6-phosphate deaminase, 3.5.99.6; GNPNAT, glucosamine 6-phosphate *N*-acetyltransferase, 2.3.1.4; GPI, glucose-6-phosphate isomerase, 5.3.1.9; NOS, nitric oxide synthase, 1.14.13.39; OCD, ornithine cyclodeaminase, 4.3.1.12; OCT, ornithine carbamoyltransferase, 2.1.3.3; ODC, ornithine decarboxylase, 4.1.1.17; PFK, phosphofructokinase (pyrophosphate-based), 2.7.1.90; PGAM, phosphoglycerate mutase, 5.4.2.1; PGD, phosphogluconate dehydrogenase, 1.1.1.44; PGK, phosphoglycerate kinase, 2.7.2.3; PGM, phosphoglucomutase, 5.4.2.2; PGM3, phosphoacetylglucosamine mutase, 5.4.2.3; PK, pyruvate kinase, 2.7.1.40; PRO-S, prolyl-tRNA synthetase, 6.1.1.15; PRPPS, phosphoribosylpyrophosphate synthetase, 2.7.6.1; RBKS, ribokinase, 2.7.1.15; RPE, ribulose-phosphate 3 epimerase, 5.1.3.1; RPI, ribose-5-phosphate isomerase, 5.3.1.6; TKT, transketolase, 2.2.1.1; TPI, triose phosphate isomerase, 5.3.1.1; UAE, UDP-*N*-acetylglucosamine 4-epimerase, 5.1.3.7; UAP, UDP-*N*-acetylglucosamine diphosphorylase, 2.7.7.23.

homologs in other organisms (fig. S3). We generated protein alignments for 1518 proteins and scored the alignments for the presence of insertions in the giardial protein relative to others. We found in-frame amino acid insertions in 44 ORFs (not attributable to alignment ambiguities) with an average of 1.5 insertions per ORF. The insertions ranged in size from 8 (our lower cutoff value) to 101 amino acids, with an average of 20. To determine whether this was an unusually high frequency, we examined 54 protein alignments, for which sequences were available from several other eukaryotes (*Chlamydomonas*, *Cryptococcus*, *Dictyostelium*, *Encephalitozoon*, *Entamoeba*, *Leishmania*, *Mus*, *Phytopthora*, *Plasmodium*, *Saccharomyces*, *Thalassiosira*, *Trichomonas*, and *Trypanosoma*; Supporting Online Material). *Giardia* sequences showed 15 insertions in 11 of the 54 proteins; the number of insertions detected for the other organisms ranged from 0 to 6 (*Plasmodium*) (Table 2). Sequence analysis of giardial cDNAs that overlap many of these insertions demonstrates that they do not represent introns. The functions of these unusual insertions remain to be determined, although when we experimentally deleted an insertion in giardial *aurora* kinase and measured protein production, we observed decreased protein stability (Supporting Online Material).

Table 2. Amino acid insertions detected in alignments of conserved proteins.

Organism	Proteins	Total no. of insertions*	Insertion size range (amino acids)
Chlamydomonas	Ribosomal protein S13, DNA-directed RNA polymerase subunits	4	21–434
Cryptococcus	Rad51, Dmc1b, serine palmitoyl transferase, guanosine triphosphate (GTP)–binding protein	4	9–44
Dictyostelium	Ribosomal protein L9, DNA-directed RNA polymerase subunit, DNA topoisomerase II	3	18–464
Encephalitozoon	ATP-dependent RNA helicase, DNA-directed RNA polymerase subunit	2	8
Giardia	Tyrosyl-tRNA synthetase, tryptophanyl-tRNA synthetase, U5 small nuclear riboprotein, ubiquitin activating enzyme E1, poly(A) polymerase, DnaK, MCM3, DNA-directed RNA polymerase subunits, RNA helicase, nucleolar GTP-binding protein, DNA topoisomerase II	15	8–81
Leishmania	Tryptophanyl-tRNA synthetase, RNA helicase, MCM3, DNA topoisomerase II	4	15–47
Mus	RNA helicase	1	26
Plasmodium	Ubiquitin-activating enzyme E1, serine palmitoyl transferase, GTP-binding protein, DNA-directed RNA polymerase subunit, vacuolar ATPase subunit, RNA helicase	6	12–86
Thalassiosira	GTP-binding protein, DNA topoisomerase II, TCP-1 chaperonin subunit γ	3	8–13
Trichomonas	26S proteasome subunit, γ-tubulin	2	8
Trypanosoma	U5 snRP, GTP-binding protein, RNA helicase	5	8–18

*Multiple insertions occurred in some proteins.

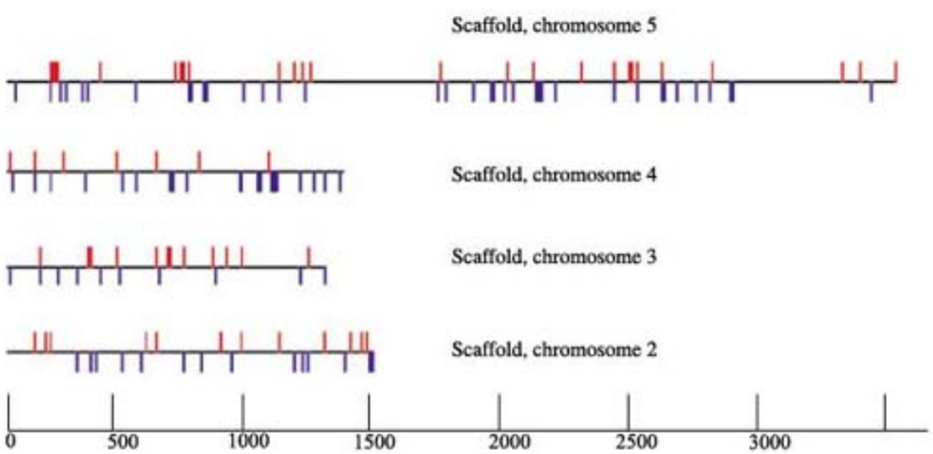

Fig. 3. Locations of VSP and other high-cysteine proteins on assembly scaffolds. From the top, scaffolds are from chromosome 5, chromosome 4, chromosome 3, and chromosome 2. Red lines indicate high-cysteine proteins (HCNCp, HCMp, HCp) and blue lines indicate VSPs. The *x* axis is scaled in kilobase pairs.

Giardial trophozoites survive in an environment of host digestive enzymes and bile. A dense single molecular layer of a variant-specific surface protein (VSP) covers the membrane and likely protects the trophozoites. Clonal VSPs on individual trophozoites switch to new VSPs every 6 to 13 generations (*31*). VSPs vary in sequence and size; all are cysteine-rich (about 12%) with frequent CXXC motifs. Each has an N-terminal signal peptide and characteristic C terminus including a membrane-spanning region terminating in CRGKA and an extended polyadenylation signal. Unlike surface proteins associated with immune evasion in other parasitic protists (*32*), giardial VSP genes distribute to many noncontiguous locations on all chromosomes (Fig. 3), and they are activated or inactivated in situ with no evidence for associated rearrangement or sequence alteration. VSPs occur at only two of the telomeres where they are truncated by TTAGG telomeric repeats, suggesting that they are pseudogenes. We estimate *Giardia*'s VSP repertoire at 235 to 275 genes (table S5). VSPs frequently cluster as two to nine genes in head-to-tail orientation. Intergenic distances between members of a cluster can be very short, with the 5′ end of one VSP overlapping with the 3′ end of a second.

In addition to the VSPs, we found two other classes of cysteine-rich proteins (Fig. 3) (*33*). There are 61 HCMps (high-cysteine membrane proteins) with 10% or more cysteine and 20 or more CXXC or CXC motifs. They lack the CRGKA tail, and their single membrane-spanning domain diverges from the VSPs. No additional leucine-rich repeat cyst wall proteins (CWPs), beyond those previously identified, were found.

Giardia encodes 149 proteins that are promising drug targets, as defined by Hopkins and Groom (*34*). As might be expected, these include a large subset of the kinases, e.g., TOR (target of rapamycin) (table S6).

When attached to the surface of the intestinal mucosa, *Giardia* trophozoites have ample opportunity to pick up genes from bacteria and to scavenge products of host and bacterial metabolism. Like that of both *Trichomonas* and *Entamoeba*, *Giardia*'s genome contains many lateral gene transfer (LGT) candidates, indicating that LGT has played an important role in shaping *Giardia*'s genome and metabolic pathways. We initially identified ORFs with similarity to bacterial or archaeal proteins at a BLAST significance level of e^{-10} or better within the top 10 hits. Of these, ~100 had multiple bacterial or archaeal homologs at a significance level of e^{-30} or better within the top 20 matches (table S3). These

include proteobacterial-like DnaK, cpn60, and cysteine sulfurtransferase (*6*, *35*). Others are NADH (nicotinamide adenine dinucleotide, reduced) oxidase and group 3 alcohol dehydrogenase, derived by LGT from a Gram-positive coccus and a thermoanaerobic bacterium, respectively (*36*). Hybrid cluster protein, A-type flavoprotein, and glucosamine-6 phosphate isomerase were recently shown to be relics of LGT (*37*). As noted, many of the enzymes in the glycolytic and pentose phosphate pathways are more similar to bacterial than to eukaryal homologs. Several ORFs had a highly significant match to an *Entamoeba* and/or *Trichomonas* protein, with the remaining matches to bacteria or archaea. Although some of these are recognized LGT relics, the rest warrant closer examination.

Cpn60, the iron-sulfur complex proteins, and DnaK are most similar to proteobacterial and mitochondrial homologs. The iron-sulfur cluster proteins and cpn60 are demonstrably targeted to the recently discovered mitosome, believed to be a relict mitochondrion (*5*). Other genes with homology to mitochondrially targeted genes are detectable, e.g., a mitochondrial protein peptidase homolog, but none have phylogenetic affinity specifically to the α-proteobacteria/mitochondrial lineage. *Giardia* is impoverished with respect to genes that are phylogenetically linked to α-proteobacteria, unlike other eukaryotes in which up to 20% of mitochondrially targeted proteins show such ancestry (*38*).

Phylogenetic inference alone cannot resolve *Giardia*'s evolutionary history. Because so many of *Giardia*'s genes may have been derived from horizontal transfer or be subject to accelerated evolution, only a subset can be used to infer phylogeny. Of the ~1500 genes for which there are known homologs, only a handful included diverse eukaryotic taxa and generated robust trees, largely because the sequences could not be unambiguously aligned. We generated and examined trees for many conserved proteins, and selected ribosomal proteins for a multigene data set because they are an ancient family, whose nature—interaction with rRNAs and with all cellular proteins during their synthesis—constrains their divergence. Phylogenetic relationships were assessed with Bayesian and maximum-likelihood statistical procedures (Supporting Online Material).

The resulting tree (fig. S4) and an earlier analysis based on 100 genes (*39*) support the deep divergence of *Giardia* and *Trichomonas* in the eukaryotic tree. Only *Encephalitozoon* branches earlier in this tree. The preponderance of molecular data place microsporidia as derived relatives of fungi, on the basis of both gene trees and ultrastructural features (*40*). *Giardia* has no such affiliation with another eukaryotic lineage. Genome-scale data from other excavate taxa (*41*) are needed to resolve whether *Giardia* and *Trichomonas* branch deeply because that is their correct position or simply because of "long branch attraction."

As discussed earlier, *Giardia* consistently shows a pattern of simplified molecular machinery, cytoskeletal structure, and metabolic pathways compared to later diverging lineages such as fungi and even *Trichomonas* or *Entamoeba* (Supporting Online Material; table S7 and fig. S5). A parsimonious explanation of this pattern is that *Giardia* never had many components of what may be considered "eukaryotic machinery," not that it had and lost them through genome reduction as is evident for *Encephalitozoon*. Taking a whole-evidence approach, one sees that these data reflect early divergence, not a derived genome.

Because *Giardia* has two nuclei, a high level of heterozygosity could accumulate in the genome. Notably, heterozygosity in the genome was estimated to be less than 0.01%. We examined the two largest contigs, representing >1.2 Mbp (10% of the genome) containing 482 single-copy genes, for high-quality mismatches between individual reads and the consensus (table S8). We found only 25 in total, eight of which were in coding regions. This suggests that there may be a biological mechanism for maintaining genome fidelity and reducing heterozygosity between the four genome copies. Meiosis-associated proteins are present in *Giardia* (*42*), although they may have alternative functions.

Giardia is an excellent functional and genomic model for other intestinal protozoan parasites whose complete life cycles cannot be replicated in the laboratory. In many pathways that require multiprotein complexes, it is notable that *Giardia* has fewer recognizable components than other organisms. Whether due to early divergence or genomic reduction, the genome gives valuable clues to the minimal components needed for complex cellular processes. The genome sequence has revealed much but also raised intriguing questions for further study, e.g., the number and distribution of introns and the composition of the giardial spliceosome, how *Giardia* maintains homozygosity across the separated nuclei, and the function of the novel genes and gene families discovered. The anticipated release of a draft genome from the related *Spironucleus vortens*, a commensal or opportunistic parasite of angelfish, will enable comparative genomics within the diplomonads and reveal which features of the giardial genome result from its obligate parasitic life-style and which reflect its basal evolutionary position.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/317/5846/1921/DC1
Materials and Methods
Figs. S1 to S5
Tables S1 to S8
References

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Whole-Genome Shotgun Sequencing of Mitochondria from Ancient Hair Shafts

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Although the application of sequencing-by-synthesis techniques to DNA extracted from bones has revolutionized the study of ancient DNA, it has been plagued by large fractions of contaminating environmental DNA. The genetic analyses of hair shafts could be a solution: We present 10 previously unexamined Siberian mammoth (*Mammuthus primigenius*) mitochondrial genomes, sequenced with up to 48-fold coverage. The observed levels of damage-derived sequencing errors were lower than those observed in previously published frozen bone samples, even though one of the specimens was >50,000 ^{14}C years old and another had been stored for 200 years at room temperature. The method therefore sets the stage for molecular-genetic analysis of museum collections.

Short fragments of mitochondrial DNA (mtDNA) have been the predominant genetic marker applied to phylogenetic and population-genetic studies of ancient samples (*1*–*3*). Although the use of complete mitochondrial genomes would provide greater analytical power, the degraded state of ancient DNA (aDNA) has prevented recovery and assembly of the full genome by conventional genetic methods. Although aDNA has been applied to phylogenetic questions for more than 20 years (*4*), only six complete mitochondrial genomes from ancient samples have been explicitly published: four from extinct moa species—*Emeus crassus* (two genomes), *Anomalopteryx didiformis*, and *Dinornis giganticus* (*5*, *6*)—and two from extinct woolly mammoth (*Mammuthus primigenius*) specimens (*7*, *8*).

Despite the field's slow start, recent developments in DNA amplification, sequencing, and analysis technologies have begun to revolutionize aDNA research, enabling the application of whole-genome shotgun sequencing approaches to a variety of aDNA sources. Recent applications of such approaches have demonstrated that nuclear DNA sequence (nuDNA), in addition to mtDNA, can be recovered and analyzed. For example, Noonan *et al.* (*9*) obtained more than 25,000 base pairs (bp) of nuDNA from a 40,000-^{14}C-year-old cave bear (*Ursus spelaeus*) bone. Using the recently developed sequencing-by-synthesis (SBS) technology (*10*), Poinar *et al.* (*11*) determined 13 million bp (Mbp) of nuDNA from a 28,000-^{14}C-year-old mammoth bone. The success of this study rapidly paved the way for application of SBS to extinct hominid samples and resulted in 1 Mbp of nuDNA from Neandertal bones (*12*, *13*). These reports have set the stage for a new era in aDNA research, but difficult challenges remain. For example, only one of these studies—the one that used exceptionally well-preserved frozen mammoth bone (*11*)—yielded sufficient quantities of endogenous DNA (i.e., DNA derived from the host and not bacterial, human, or other external contaminants) to make it economical to sequence entire nuclear genomes of extinct species.

Hair shafts are a promising source of aDNA. Long-term hair survival occurs in a variety of natural environments, and large quantities are present in taxonomic collections representing most extant, and many recently extinct, mammalian taxa. Most hair-based genetic studies have used roots, instead of shafts, as a DNA source (*14*), primarily because hair shafts comprise dead keratinized cells that contain relatively low levels of DNA. However, several studies have reported shafts as a viable source of modern (*15*) and ancient (*16*) mtDNA. Furthermore, several properties of shafts suggest that they constitute an attractive DNA source for SBS. First, their relative abundance (when present) renders them preferable to bones, because the destructive nature of sampling can lead to the loss of important morphological information. Second, turnover of keratinocytes in the hair bulb is exceedingly high, second only to that of the cells of the gut epithelium (*17*). Therefore, baseline mitochondrial levels in these cells (and thus the precortical cells that develop into the bulk of the shaft) may be higher than those in other tissues commonly used for aDNA analyses. Third, even when degraded, shafts are resistant to contamination from exogenous DNA such as bacteria, blood, and skin cells (*16*, *18*). We demonstrate here that hair shafts surpass comparably stored bone as an aDNA source for use in SBS approaches, in regard to preservation and concentration of mtDNA.

We successfully extracted sufficient DNA for SBS from 10 samples of mammoth coat-hair shafts, collected from permafrost deposits spanning northern Siberia [Table 1, Fig. 1, and supporting online material (SOM) text]. Due to the pilot nature of this study, we used as much hair as was readily available (0.2 to 5.2 g per extraction). The degradation of aDNA correlates exponentially with temperature (*19*), thus DNA survival depends on sample age and the storage history (including the time and temperature at which it has been stored pre- and postcollection). Surprisingly, we successfully extracted DNA from the sample (M13) that had been at room temperature for the longest period and that had the lowest amount of material available [0.2 g, in comparison to 0.75 and 1 g bone (*7*, *11*) and up to 0.4 g frozen muscle (*8*) used in the previous studies]. Although hair morphology varies significantly both between species (*20*), and among hair types on individuals, and thus the general applicability of this method remains to be shown, previous studies have demonstrated successful recovery of DNA from a variety of modern hair types and species (SOM text). Thus, this method will likely be widely applicable.

The combined use of hair shafts and SBS resulted in 10 full mitochondrial genome sequences, with 7.3- to 48.0-fold coverage (Table 1). The sequences are complete, except that we have not tried to assemble the variable number of tandem repeats (VNTR), which is

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Table 1. Description of mammoth mitochondrial sequences, including the year that the sample was discovered, where known; the ^{14}C reference of specimens dated in this study; the percentage of mitochondrial sequences among SBS sequences; the number of contigs assembled out of mitochondrial sequences; the average read length before trimming, based on Krause (*7*) sequence; the average percentage identity with respect to assembly after automatic computational quality processing (i.e., the final read used in alignment); and the percentage difference from M1 sequence. nd, not determined.

Sample	Tissue	^{14}C date	Year collected	OxA ^{14}C reference	Sequencing technology	% Mitochondrial	Contigs	Fold coverage	Average untrimmed read length	% C→T damage	% Trimmed read identity	% Diff vs. M1
M1	Hair	nd	nd		454	1.99	1	48.0	119.0	0.243	99.86	0.00
M2 (Jarkov)	Hair	20,380 ± 140	1997		454	0.76	1	13.2	99.5	0.427	99.79	0.09
M3 (Fishhook)	Hair	20,620 ± 70	1990		454	1.21	1	20.3	128.1	0.347	99.82	0.03
M4	Hair	18,545 ± 70	nd	17098	454	0.65	1	7.8	75.9	0.314	99.85	0.16
M5	Hair	nd	nd		454	1.30	1	19.8	112.6	0.537	99.76	0.15
M8 (Dima)	Hair	46,900 ± 700	1977	17102	454	1.43	1	27.7	71.1	0.899	99.60	0.14
M13 (Adams)	Hair	35,800 ± 1200	1799/1806		454	0.76	1	19.1	60.5	0.713	99.73	0.09
M18	Hair	17,125 ± 70	nd	17116	454	1.50	1	24.6	129.8	0.388	99.83	0.05
M22	Hair	50,200 ± 900	2000	17111	454	2.09	1	17.0	96.8	0.556	99.72	0.17
M26	Hair	24,740 ± 110	2003	17114	454	0.46	1	7.3	91.2	0.253	99.84	0.22
Poinar	Bone	27,740 ± 220	2005		454	0.08	2	7.7	101.1*	1.699	99.51	0.09
Rogaev	Muscle	33,750 to 31,950			Sanger	nd	nd	nd	nd	nd	nd	0.21
Krause	Bone	12,170 ± 50			Sanger	nd	nd	nd	nd	nd	nd	0.13

*The sequencing technology (Roche GS 20) used for the generation of the Poinar (*11*) sequence precluded obtaining longer average read length.

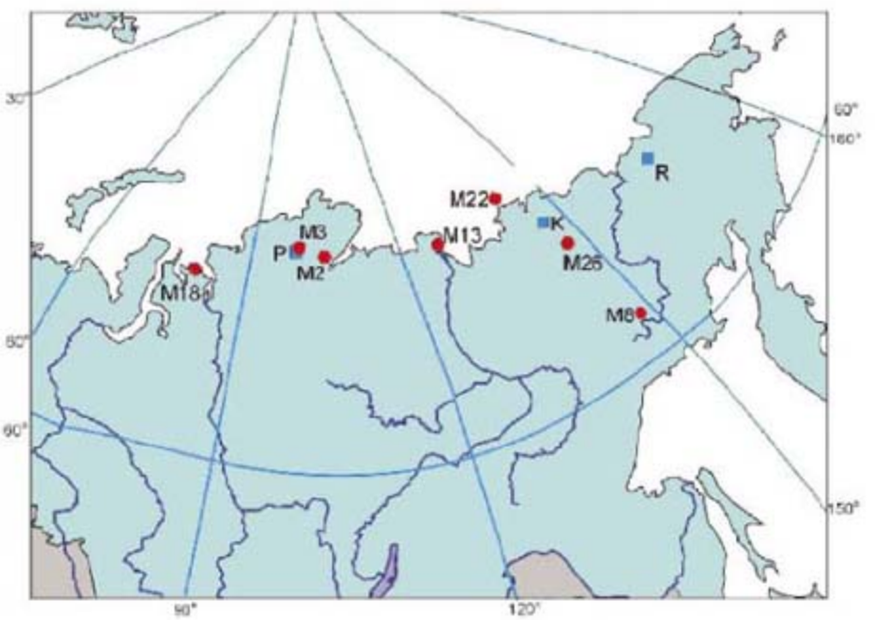

Fig. 1. Sites of recovery of the mammoth hair specimens whose mitochondrial genome sequences are reported here. The locations of M1, M4, and M5 are not known, but most probably originate from Northern Yakutia (about 66° to 76°N, 106° to 160°E). Recovery sites for other mitochondrial genomes used in this study—Krause (*7*), Rogaev (*8*), and Poinar (*11*, *21*)—are indicated as blue squares labeled K, R, and P, respectively.

difficult to sequence [even with polymerase chain reaction (PCR) and sequencing (*8*)] or to align with any certainty. For example, in the sequence of Krause *et al.* (*7*), this region of the mammoth mitochondrial genome is 320 bp, whereas it is 393 bp in the sequence of Rogaev *et al.* (*8*), so comparison of these regions is essentially uninformative. Overall, the yield of mtDNA sequence was 5.75 to 26 times as high as that from the permafrost-preserved bone reported previously (*11*, *21*), supporting previous hypotheses that in comparison to bone, the ratio of mtDNA to nuDNA in the hair shaft is elevated (*16*, *22*).

Three widely recognized difficulties are associated with sequencing aDNA: DNA damage, sequencing errors, and numts. Numts are mitochondrial sequences that were inserted into the nuclear genome during genome evolution after duplication and may cause artifacts in PCR-based studies or shotgun assemblies with low coverage. Our approach solves all of these problems through the high redundancy of our sequencing and the fact that SBS targets unique, individual DNA template molecules.

We assessed the state of DNA preservation through two parameters—untrimmed read length and DNA damage [cytosine-to-thymine (C→T) miscoding lesions, derived from the hydrolytic deamination of cytosine to uracil, observed in the pyrosequencing data] (*21*, *23*). The sizes of unbroken aDNA fragments could be measured because the study was conducted on a SBS instrument (Roche GS FLX) that can generate reads up to a length of 250 bp. We observed an average sample-dependent mitochondrial read length between 60.5 and 128.1 bp. The previously described average read length of 101 bp from a bone sample (*11*) was limited by the instrument read length (Roche GS20), leaving open the possibility that the bone sample retained longer fragments of mtDNA than those that we observed. However, comparing the individual reads versus locations in the assembly consensus sequence containing C, the hair-generated data show a substantially improved (i.e., lower) C→T DNA damage rate of 0.24 to 0.9% versus 1.7% in bone. In contrast to the bone, which was kept frozen for the entire period postexcavation from the permafrost, most of the hair samples have been at room temperature for a number of years (Table 1).

To investigate what effect this might have on the DNA preservation of the samples, we calculated approximate thermal ages (*19*) of those specimens for which we knew or could estimate sufficient information for the calculation [including for comparison the Poinar mammoth (*11*)]. The model incorporated temperature data from weather stations local to the respective sites, with altitude correction (lapse rate of +6.5°C km^{-1}) that used elevations estimated from the sample coordinates (with the use of GoogleEarth v.4.1). Furthermore, to control for differences in sample burial depth (and thus temperature of the burial site), the model incorporated two depths of burial for each sample—shallow (where the sample temperature could be expected to fluctuate during the year) and deep (where the sample would experience a con-

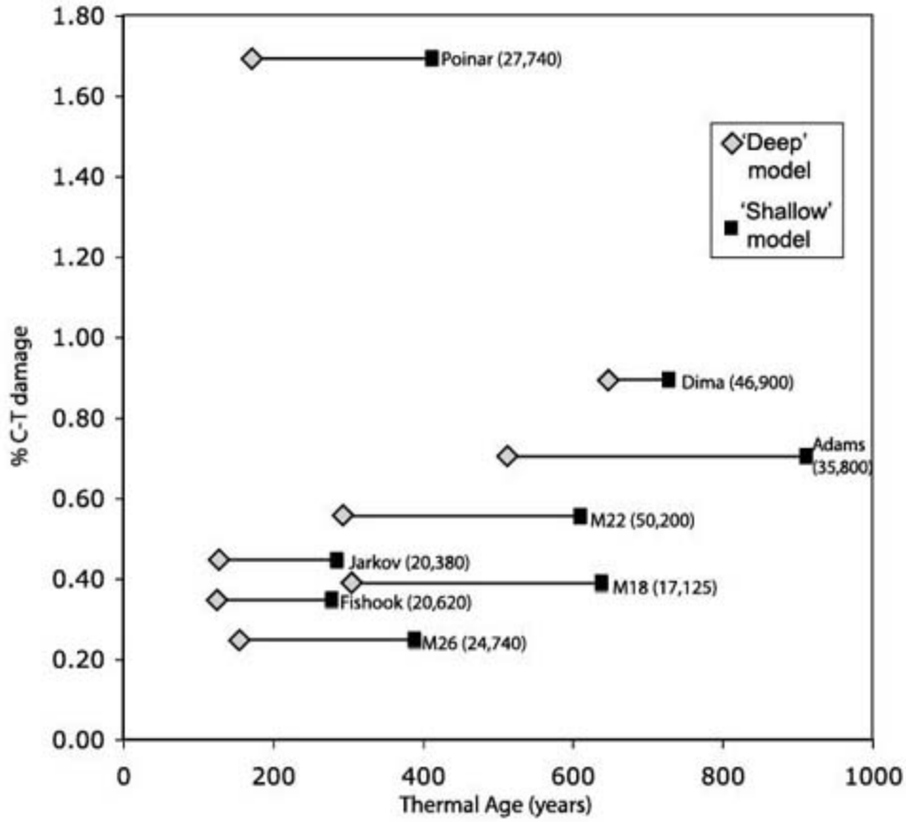

Fig. 2. Comparison of estimated thermal age of samples against percentage C-T damage with the use of alternative temperature models for Siberia (reflecting the range of published estimates). Approximate thermal ages were calculated according to the methods of Smith *et al.* (*19*) for mammoths for which sufficient information was known, with the use of two alternative burial models. The mean ^{14}C age for each sample is also shown.

stant temperature)—and factored in time and temperature (at a conservative assumption of 10°C) since collection (*19*) (Fig. 2 and SOM text).

The data indicates that although the approximate thermal ages of several of the samples are older than the Poinar mammoth, their numbers of damaged derived miscoding lesions were lower (Fig. 2). The explanation for this remains unclear. It is possible that as hypothesized previously, hair cell keratinization protects the DNA within hair shafts from contact with free water, a requisite of the hydrolytic deamination underlying C→T damage (*16*). DNA may also be conserved because the hair, in contrast to porous bone, prevents access of bacteria to the site of DNA storage, thereby restricting the breakdown of biopolymers. Alternatively, the observation may be explained by other as-yet untested hypotheses. For example, special properties of hair shaft keratinocytes may confer advantages, such as an absence of postmortem cell autolysis; other molecules within the hair shaft (e.g., melanin) may provide protection; or the relatively unique preservation conditions that hair preservation in the archaeological record requires may in turn limit DNA degradation. Whatever the explanation, DNA degradation within the hair shafts does not appear to conform to current hypotheses about DNA degradation, and by inference the limits within which usable levels of DNA can be recovered from ancient samples may be greater than conventionally believed. This is in many ways unsurprising, given that many models of DNA degradation are based on theoretical degradation rates that were initially calculated to apply to DNA in free solution (*19*), and therefore it is plausible that their general applicability across biological tissues may not be straightforward.

Sequencing error—i.e., the difference between the (possibly damaged) molecule and the machine output—was also lower with the GS FLX. In all cases, the sum of damage plus sequencing error, as measured by the difference between the consensus sequence and the individual reads, was between 0.14 and 0.4%. Note that a C→T damage rate of 0.8% creates roughly a 0.2% component of the overall error rate, because only about one-quarter of nucleotides are C. Furthermore, although numts have been known to cause complications in mtDNA extracted from various mammalian tissues (including hair from some elephants) (*24*), a careful analysis (see SOM text for details) showed that contamination of our assemblies by numts was negligible.

Our findings have profound implications on the scope of future studies. Included in our data set are recently discovered mammoth permafrost specimens, including the Jarkov (M2), the Fishhook (M3), and the baby Dima (M8). Perhaps the most well-known sample among those we analyzed is M13, known colloquially as the Adams mammoth. This was the first mammoth to be scientifically studied, and the resulting documentation showed beyond reasonable doubt that an animal species can go extinct. The almost perfectly preserved permafrost mummy was found in 1799 by a hunter of the Tungus tribe, who collected its tusks in the summer of 1804 and eventually helped the Russian botanist Michael Adams to collect the remainder of the specimen in 1806. To this date, the Adams skeleton is one of the most complete, and it has been continuously on display at the Zoological Museum in St. Petersburg (*25*). In the process of recovering the entire skeleton, large amounts of hair, a total of 36 pounds (16.4 kg), were taken to St. Petersburg and distributed to other institutions around the world for investigation. The hair specimens have been stored for the past 200 years at room temperature, similar to most other samples that might be available for future analysis. Notably, even though these storage conditions are not optimal for DNA preservation (*19*), we were able to obtain a complete mitochondrial sequence from this specimen with the use of our whole-genome shotgun method, on no more than 0.2 g of hair shaft. The finding that aDNA can be extracted from a specimen kept at room temperature for two centuries puts a large number of collections stored in natural history museums within reach of molecular genomic analysis and may allow us to add molecular-genetic data to the collections of Charles Darwin, Alexander von Humboldt, and Carl von Linné.

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SOM Text
Figs. S1 and S2
Tables S1 and S2
References

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Structures of the CCR5 N Terminus and of a Tyrosine-Sulfated Antibody with HIV-1 gp120 and CD4

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The CCR5 co-receptor binds to the HIV-1 gp120 envelope glycoprotein and facilitates HIV-1 entry into cells. Its N terminus is tyrosine-sulfated, as are many antibodies that react with the co-receptor binding site on gp120. We applied nuclear magnetic resonance and crystallographic techniques to analyze the structure of the CCR5 N terminus and that of the tyrosine-sulfated antibody 412d in complex with gp120 and CD4. The conformations of tyrosine-sulfated regions of CCR5 (α-helix) and 412d (extended-loop) are surprisingly different. Nonetheless, a critical sulfotyrosine on CCR5 and on 412d induces similar structural rearrangements in gp120. These results now provide a framework for understanding HIV-1 interactions with the CCR5 N terminus during viral entry and define a conserved site on gp120, whose recognition of sulfotyrosine engenders posttranslational mimicry by the immune system.

Entry of human immunodeficiency virus type 1 (HIV-1) into host cells requires its gp120 envelope glycoprotein to bind to two cell-surface receptors, CD4 and a co-receptor, either CCR5 or CXCR4 [reviewed in (*1*, *2*)]. CCR5 and CXCR4 are members of a family of chemokine receptors that are G protein–coupled receptors (*3*) characterized by seven transmembrane helices, an extracellular N terminus, which is variable in length, and three extracellular loops (ECLs) (Fig. 1A). The structure of the co-receptor has not been determined, but some insight has come from the crystal structures of other family members (*4*).

Elements critical to interactions with HIV-1 are located in the co-receptor N terminus and around its second extracellular loop (ECL2) (*5*–*8*). The co-receptor N terminus interacts with a highly conserved 4-stranded bridging sheet in gp120, which assembles upon CD4 binding, whereas the ECL2 region of the co-receptor interacts with the tip of the immunodominant V3 loop in gp120. Considerable distance separates these two interactive regions, which suggests that they are independent (*9*–*12*).

The N-terminal interaction of co-receptor with HIV-1 requires an unusual posttranslational modification, *O*-sulfation of tyrosine (*13*). On CCR5, tyrosines at residues 3, 10, 14, and 15 may be *O*-sulfated, but sulfations at residues 10 and 14 are sufficient to facilitate interaction with HIV-1 (*14*). Interestingly, many CD4-induced antibodies that react with the bridging sheet region are also modified by *O*-sulfation (*15*). To define structurally the interaction of HIV-1 with the N terminus of CCR5 and to understand the molecular details of the mimicry of this interaction by CD4-induced antibodies, we used a combination of nuclear magnetic resonance (NMR) and x-ray crystallography to determine the structures of the N terminus of CCR5 and of a functionally sulfated antibody, 412d, in complex with HIV-1 gp120. Analysis of these structures, combined with molecular docking and saturation transfer difference NMR, identified a conserved site on gp120, which recognizes sulfotyrosine with high selectivity.

We used NMR techniques that exploit the transfer of information from bound to ligand-free states (*16*, *17*) to analyze the interactions of a 14-residue peptide ($CCR5^{2\text{-}15}$), which consisted of residues 2 to 15 of CCR5 with sulfotyrosine (Tys) at positions 10 and 14 (Fig. 1) (*18*). We collected two-dimensional (2D) nuclear Overhauser enhancement spectroscopy (NOESY) spectra of solutions containing $CCR5^{2\text{-}15}$ either free or in the presence of gp120, CD4, or a gp120-CD4 complex (peptide:protein ratio of 40:1). Whereas spectra containing free $CCR5^{2\text{-}15}$ or $CCR5^{2\text{-}15}$ with either gp120 or CD4 contained few cross peaks, $CCR5^{2\text{-}15}$ in the presence of the gp120-CD4 complex gave rise to high-quality spectra containing numerous NOEs (Fig. 1B and fig. S1). Complete ^{1}H, ^{13}C, and ^{15}N assignments of $CCR5^{2\text{-}15}$ (table S1) were made on the basis of standard 2D homonuclear and heteronuclear NMR experiments that measure scalar and dipolar couplings.

The NOESY data of $CCR5^{2\text{-}15}$ in the presence of gp120-CD4 (Fig. 1B) were sufficient for calculating a high quality ensemble of NMR structures (Fig. 1C). Structure calculations were carried out on the ordered region comprising residues 7 to 15. A total of 70 distance restraints (corresponding to 35 intraresidue and 35 interresidue NOEs), and 56 dihedral angle restraints were included in the final round of structure calculations, which gave rise to an ensemble of 40 structures with a backbone root-mean-square deviation (rmsd) of 0.46 Å and an rmsd of 1.39 Å for all atoms in the ordered region (residues 9 to 14) (table S2). Superpositions of the final ensemble defined a helical conformation for residues 9 to 15, which deviated from the ideal by a backbone rmsd of only 0.26 Å (Fig. 1D). Sulfotyrosines 10 and 14 extended from the same face of the helix, with sulfate moieties separated by ~10 Å and an ~90° rotation around the helix axis.

We were unable to obtain crystals of $CCR5^{2\text{-}15}$ in complex with HIV-1 gp120-CD4, and the size and glycosylation of the ternary complex hindered direct determination by NMR. We were, however, able to obtain ~3.5 Å diffraction from crystals of the antigen-binding fragment (Fab) of the 412d antibody, in complex with gp120 (core with V3, CCR5-dependent isolate YU2) and CD4. The 412d antibody is functionally tyrosine-sulfated, binds to a CD4-induced epitope that overlaps the site of co-receptor binding on HIV-1 gp120, and recognizes preferentially CCR5-dependent strains of HIV-1 gp120 (*15*). Moreover, the tyrosine-sulfated region of 412d can be sub-

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stituted for the tyrosine-sulfated region of CCR5 to create a chimeric 412d/CCR5 receptor that supports HIV-1 entry (*19*).

We solved the 412d-gp120-CD4 structure by molecular replacement. Despite less than optimal resolution and completeness, initial unbiased maps showed clear definition of important antibody features (fig. S2). Structure refinement resulted in an R_{cryst} of 20% (R_{free} 27%) (Fig. 2, table S3, and fig. S3). The overall mode of binding of 412d resembles that of 17b, which shares a heavy chain of similar genomic origin (fig. S4) (*20*). A hydrophobic interaction pins the second complementarity-determining region of the heavy chain (CDR H2) to a conserved hydrophobic surface on the bridging sheet of gp120, whereas the acidic CDR H3 binds a basic gp120 surface. Antibody 412d, however, interacts with a much larger overall surface area than either 17b or X5 (fig. S4). The increased 412d interaction surface is due primarily to an increase in buried surface associated with its CDR H3. Comparison of free (*20*) and bound structures of 412d shows that extensive ordering occurs in CDR H3 when bound to gp120 (fig. S5).

The two sulfotyrosines in the CDR H3 region of 412d bind to gp120 in quite different ways (Fig. 2). The sulfotyrosine at residue 100 of 412d (Tys 100^{412d}) [Kabat numbering (*21*)] is mostly exposed, with its aromatic ring making π-cation interactions with the guanidinium of Arg 327^{gp120} and its sulfate group making only peripheral electrostatic interactions. By contrast, the side-chain of Tys $100c^{412d}$ is mostly buried, with Ile 322^{gp120} and Ile 326^{gp120} embracing one face of the tyrosine ring, while the aliphatic base of Arg 440^{gp120} supports the other. Together, the two sulfotyrosines account for about 20% of the total buried surface on 412d, with almost 100 $Å^2$ derived from Tys $100c^{412d}$.

To facilitate interactions with the sulfotyrosines in 412d, the V3 stem is rearranged. The conserved Arg 298^{gp120} and Pro 299^{gp120} at the base of the V3 loop are mostly unchanged, but the subsequent Asn residues at 301^{gp120} and 302^{gp120} shift ~7 Å to form one wall of the Tys $100c^{412d}$ sulfate-binding pocket. Residue 301^{gp120} is N-glycosylated, but the glycan faces solvent, and its presence should have little impact on the ability of the binding pocket to form. Meanwhile, in the returning strand (*22*), Ile

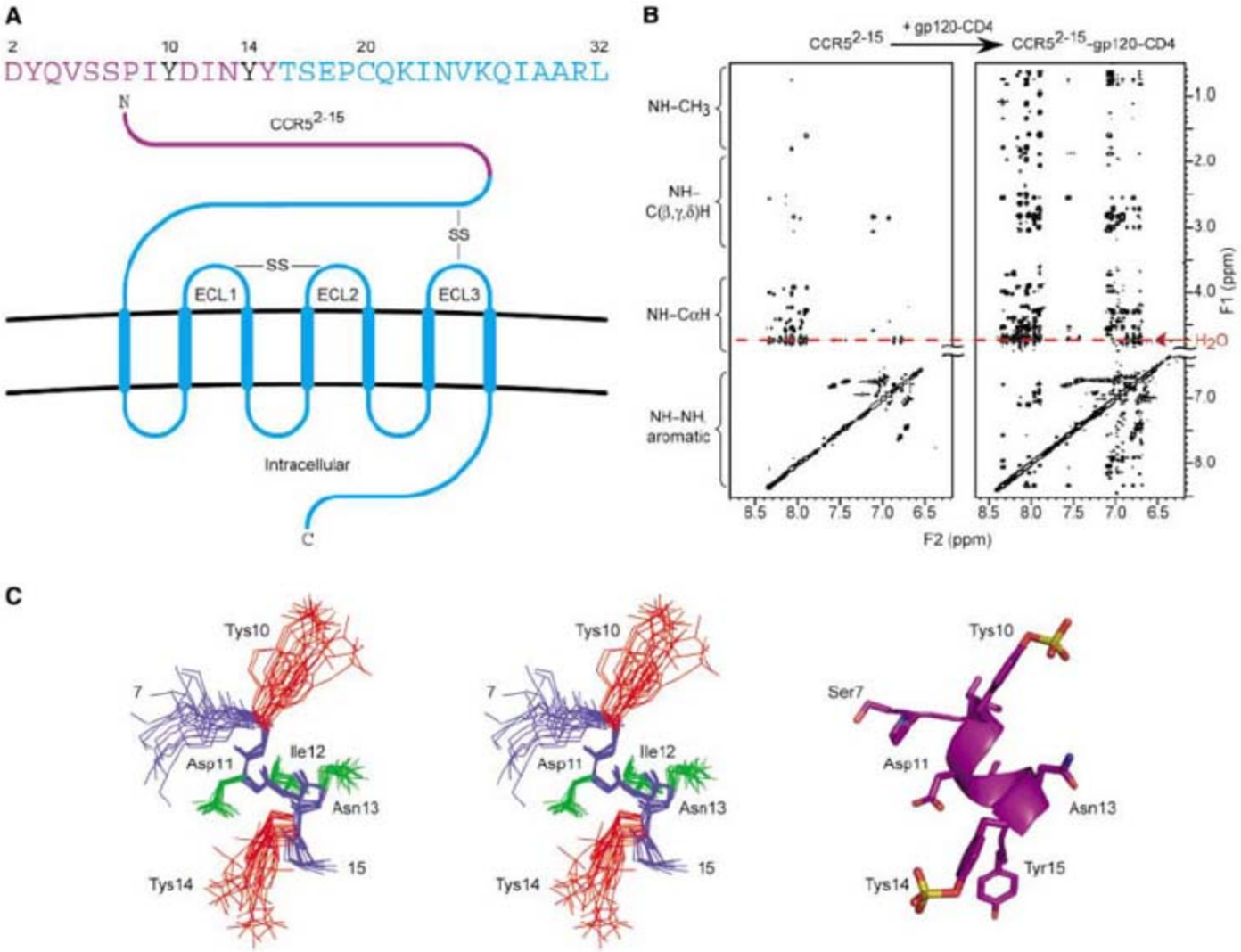

Fig. 1. Structure of the tyrosine-sulfated N terminus of CCR5 in the gp120-bound conformation. **(A)** CCR5 sequence and schematic of its insertion in the cell membrane. Sequence letters in purple correspond to residues in $CCR5^{2-15}$, with sulfotyrosines (Tys) critical for interaction with HIV-1 highlighted in black. ECLs are labeled, and disulfide bridges (-SS-) depicted. **(B)** 2D NOESY spectra for $CCR5^{2-15}$ free in solution (left) and in the presence of gp120–CD4 (right). NMR samples (20 mM phosphate, 50 mM NaCl, pH 6.85) contained 800 μM $CCR5^{2-15}$ in the presence of 20 μM gp120-CD4 and were recorded at 500 MHz, 300 K, mixing time = 150 msec. Sequential NH(*i*)–CαH(*i*-1) NOEs were observed between every residue, thereby confirming sequential assignments, and predicted intraresidue NOEs were observed for all residues. No correlations beyond sequential NOEs were observed between residues 2 and 7, indicating that this region of CCR5 was extended or disordered. In contrast, NOEs from CαH(*i*) to NH(*i* + 1,2,3) and from NH(*i*) to NH(*i* + 1,2,3) were observed for residues 9 to 15 (fig. S1), indicating an ordered α-helical structure (*33*). **(C)** Structure of the ordered region of gp120-bound $CCR5^{2-15}$. Stereoview (left) of 25 lowest energy-simulated annealing structures superimposed by fitting to the backbone of residues 9 to 15. Structural statistics are provided in table S2. Backbone appears in blue, amide hydrogens (9 to 15) in blue, side chains (11 to 13) in green, and Tys 10 and Tys 14 in red. Ribbon diagram (right) of restrained minimized mean structure with side chains in stick representations.

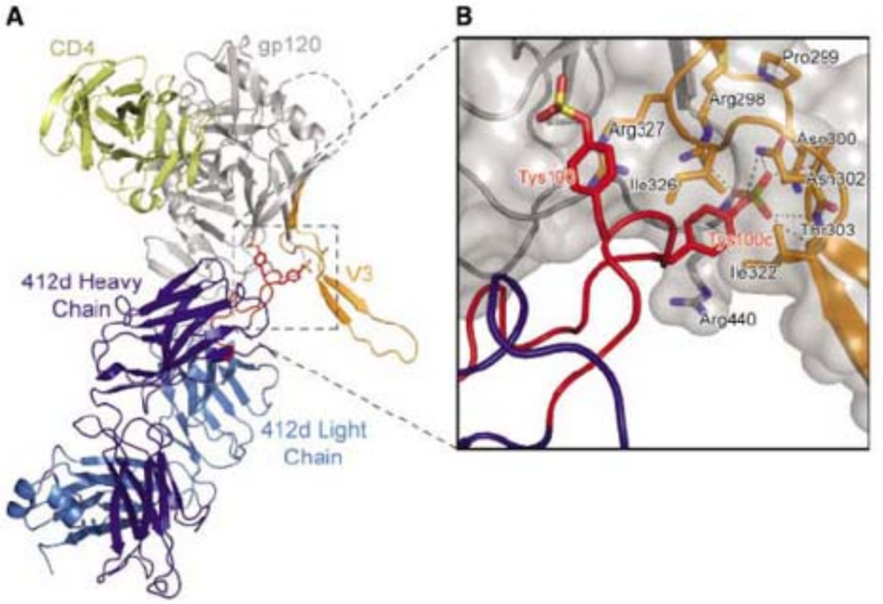

Fig. 2. Structure of the tyrosine-sulfated antibody 412d in complex with HIV-1 gp120 and CD4. **(A)** Ribbon representation. CD4 is yellow, the heavy chain of Fab 412d is dark blue, the light chain is cyan, and gp120 is gray, except for the V3 loop, which is orange. The CDR H3 loop of 412d is red, with sulfotyrosines depicted in stick representation. **(B)** Close-up, with molecular surface of gp120 in gray and sulfotyrosines of 412d (red labels) and select residues of gp120 (black labels) in stick representation. Dotted lines represent coordinating hydrogen bonds between gp120 and the sulfate group of $Tys100c^{412d}$. The sulfate of $Tys\ 100c^{412d}$ makes a full complement of ionic interactions: a salt bridge to $Arg\ 298^{gp120}$ and hydrogen bonds to the side-chain nitrogen of $Asn\ 302^{gp120}$, the side-chain hydroxyl of $Thr\ 303^{gp120}$, and the main-chain amides of 302^{gp120}, 303^{gp120}, and 441^{gp120} (*34*).

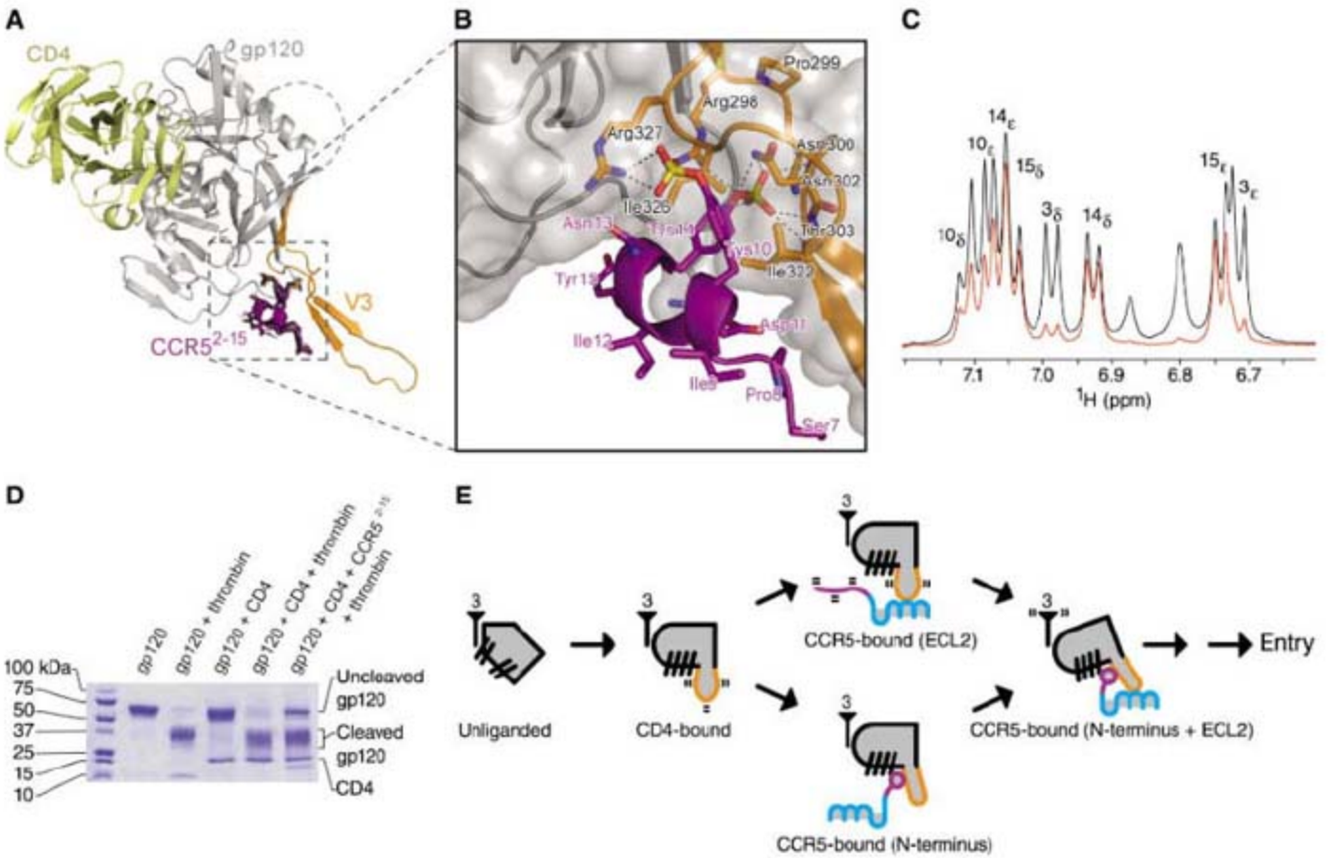

Fig. 3. Interaction of the N terminus of CCR5 with HIV-1 gp120-CD4. **(A)** Molecular docking. The 20 lowest energy structures (black) from 200 docking runs of $CCR5^{2-15}$ are shown in stick representation. Despite initial random orientations, all favorable docking solutions had Tys 14 binding at the bridging sheet-V3 interface; none had Tys 10 at this cleft. Ribbon representations illustrate CD4 in yellow, gp120 in gray (with V3 in orange), and the lowest energy structure of $CCR5^{7-15}$ in purple. **(B)** Close-up, with molecular surface of gp120 in gray and select residues of gp120 (black labels) and CCR5 (purple labels) in stick representation. **(C)** Saturation transfer difference NMR spectrum of $CCR5^{2-15}$ in the presence of gp120–CD4 (red) overlaid on a control ^1H spectrum (black). Experimental conditions were identical to those used for NOE experiments, except that the carrier was set at −1 and 50 parts per million for on- and off-resonance saturation, respectively. The intensities of the most strongly enhanced peaks (Tys 14 and Tyr 15) have been normalized to the corresponding signals in the control spectrum. Peak assignments made by 2D NMR (table S1) appear above their corresponding doublet signals. Tys 14 and Tyr 15 show strong saturation transfer difference effects, whereas Tys 10 shows a medium effect and Tyr 3 a very weak effect. These effects correlate directly with the buried surface area of each tyrosine ring in the docked structure. See fig. S9 for overlaid spectra employing 1 to 7 s saturation. **(D)** Effect of $CCR5^{2-15}$ on the proteolytic sensitivity of the V3. Electrophoresis on an 8 to 25% gradient SDS polyacrylamide gel shows the results of thrombin digestion on gp120 (core with V3; YU2 R5 strain of HIV-1) alone, or in the presence of sCD4 or sCD4 and $CCR5^{2-15}$ (*35*). **(E)** Structural intermediates of HIV-1 entry. At far left, a single monomer of unliganded gp120 (gray) is shown with separated β-hairpins. The threefold axis, from which gp41 interacts in the functional oligomer, is labeled with the number 3. In the CD4-bound state, the bridging sheet assembles, and the V3 (orange) is exposed and flexible. The next state involves either (upper pathway) the interaction of the CCR5-ECL2 region with the V3 tip or (lower pathway) the interaction of the CCR5 N terminus, which induces rigidification of the V3 stem. Engagement of CCR5 at both N terminus and ECL2 region triggers additional conformational changes leading to HIV-1 entry.

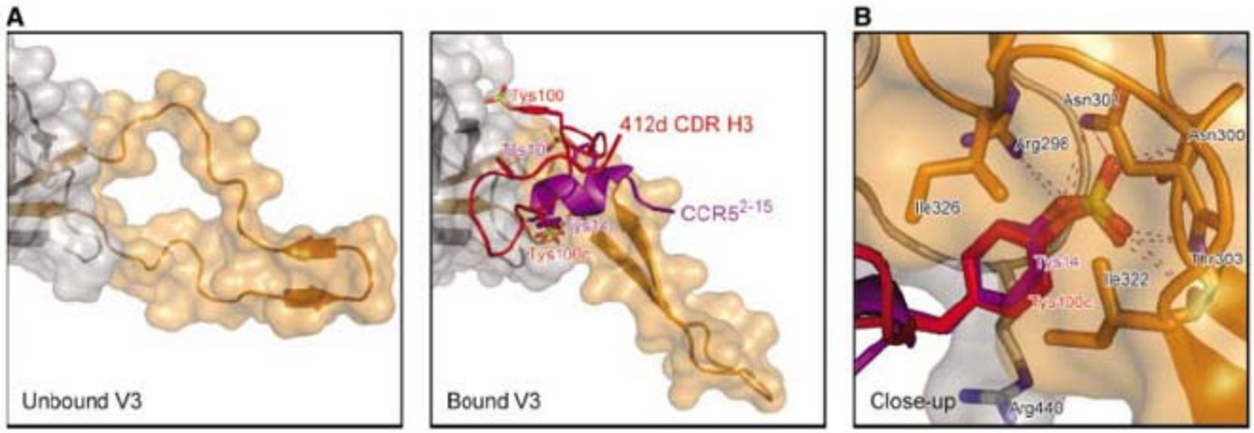

Fig. 4. A conserved site for binding sulfotyrosine on HIV-1 gp120. **(A)** Alterations of the V3 base to accommodate binding of sulfotyrosine. The gp120 (gray) region around the V3 loop (orange) is illustrated in ribbon diagram, with an overlying semitransparent surface for unbound (left panel) and bound (right panel) conformations. Binding of the CCR5 N terminus (purple) or the 412d CDR H3 (red), each with two sulfotyrosines (stick representation, with red and purple labels), alters the V3 base, forming a sulfotyrosine binding pocket and a rigid β-hairpin. **(B)** Close-up of the conserved sulfotyrosine binding pocket. The orientation shown is similar to that in Figs. 2B and 3B [~90° from (A) about a diagonal axis, as defined by the long axis of the V3 from (A)]. Tys 14^{CCR5} is shown in purple, with Tys $100c^{412d}$ in red. Select residues of gp120 are shown in stick representation and labeled in black. Hydrogen bonds coordinating the buried sulfate groups in each are depicted with dotted lines.

322^{gp120} shifts 10 Å to encase the $100c^{412d}$ tyrosine ring. Overall, the incoming and outgoing strands of the V3 stem are brought closer together, so that a β-hairpin is formed that replaces the previously flexible V3 stem (*23*). Thus, whereas most of the gp120-CD4 complex remains unchanged, binding of sulfotyrosine at the bridging sheet-V3 interface results in formation of a more rigid V3.

By employing molecular docking and saturation transfer difference NMR, we sought to use the 412d-gp120-CD4 structure to ascertain how gp120 interacts with the N terminus of CCR5. We first tested whether docking [Autodock 3.0 (*24*)] of the CDR H3 loop of 412d to gp120 would recapitulate the 412d-gp120 crystal structure. Starting from random initial positions and orientations, multiple runs of the excised CDR H3 loop (residues 97 to 100f) produced an energetically favorable interaction (–16.04 kcal/mol), which closely resembled its location and contacts in the crystal structure (Cα rmsd between crystal and docked CDR H3 was 1.03 Å) (fig. S6). We next docked the NMR structure of the CCR5 N terminus to the crystal structure of gp120-CD4. Multiple runs produced a cluster of energetically favorable solutions (–17.60 kcal/mol for the optimal solution), which placed $CCR5^{2-15}$ at the bridging sheet-V3 interface (Fig. 3, A and B). The top 10% of the solutions (20 best solutions from 200 runs) had rmsds of 1.04 Å (Cα) and 2.24 Å (all atoms).

To validate the docked CCR5-gp120 structure, we performed saturation transfer difference NMR (*17*) on $CCR5^{2-15}$ in the presence of gp120-CD4. Control and difference spectra are shown in Fig. 3C. Contact surfaces of Tys and Tyr residues of CCR5 in the docked orientation correlated well with saturation transfer difference enhancements (Fig. 3C). We also observed good correlation between interacting residues in the docked gp120-CCR5 interface and gp120 and CCR5 substitutions (*9*, *25*–*27*) that affect gp120-CCR5 binding (fig. S7).

The N terminus of CCR5 approaches from the same face of gp120 as CD4 but binds to an orthogonal surface at the intersection of the bridging sheet and the V3 loop (Fig. 3). The first CCR5 residues (Ser 7 and Pro 8) that are ordered in the NMR structure interact with the V3 stem. In the helix (residues 9 to 15), Tys 10 interacts with the gp120 core and forms a salt bridge with Arg 327^{gp120}, Asp 11 forms an ionic interaction with Arg 440^{gp120}, Tys 14 is completely sequestered in the crevice between V3 and the bridging sheet, and the aromatic ring of Tyr 15 packs against Ile 439^{gp120} on the bridging sheet.

The structural rearrangements required to form the Tys 14 binding pocket would be expected to rigidify the V3 stem. We tested V3-proteolytic susceptibility (Fig. 3D). CD4 enhances V3-proteolytic susceptibility to thrombin (*28*, *29*), whereas the combination of CD4 and $CCR5^{2-15}$ reduced proteolytic susceptibility (Fig. 3D), consistent with CCR5-rigidification of V3.

Overall, the gp120 recognition surface for $CCR5^{2-15}$ is much more highly conserved for CCR5-dependent isolates compared with those that use CXCR4. Good electrostatic complementarity is found between the acidic $CCR5^{2-15}$ and gp120, where the negatively charged C-terminal helix dipole is oriented toward the basic bridging sheet (fig. S8). The docked structure provides an explanation for the observed lack of order at the N terminus of $CCR5^{2-15}$, where CCR5 appears to extend away from gp120. At the C terminus, Tyr 15 points toward the target cell membrane where, in five residues, a disulfide would normally be made between the N terminus (Cys 20) and the third extracellular loop (Cys 269).

Despite the highly divergent tyrosine-sulfated structures of 412d and CCR5, a single sulfotyrosine (residue 100c in 412d and residue 14 in CCR5) is recognized in a similar manner by gp120 (Fig. 4). We used mutagenesis to probe the degree of similarity in this recognition (fig. S10). The alteration of a single nitrogen in a contact residue (Asn302Asp) in the conserved binding pocket ablates recognition of both 412d and CCR5, whereas a similar substitution (Asn300Asp), just outside the binding pocket, had little effect (*30*). The observed convergence of recognition likely reflects the high selectivity of this site for sulfotyrosine (a 7 Å deep pocket, with hydrophobic walls and a cationic floor, which is unlikely to interact favorably with other nonmodified amino acids). Such selectivity and favorable energetics bode well for design of therapeutics targeted at this site, because the gp120 residues that line the sulfotyrosine binding pocket are highly conserved for co-receptor binding.

The structure of the CCR5 N terminus with gp120-CD4 provides a further snapshot of the HIV-1 entry pathway (Fig. 3E). Before binding CD4, the bridging sheet is not formed and the V3 loop is occluded. Binding of CD4 induces bridging sheet assembly and V3 exposure. At this stage, the V3 is flexible and poised close to the target cell membrane. Subsequent interactions with CCR5 are still being elucidated. We show structural details for one: engagement by gp120 of the CCR5 N terminus, which requires formation of a conserved pocket for sulfotyrosine binding and converts the flexible V3 stem into a rigid β-hairpin. It will be interesting to integrate the order and timing of the rearrangements revealed here into the HIV-1 entry mechanism.

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22. Stem movements are somewhat imprecise because the returning V3 stem exhibits considerable disorder before interaction with the N terminus of CCR5 (*11*).
23. The nascent β-hairpin in the V3 stem extends ~15 Å; further extension is interrupted by a lattice contact, which occurs with the outgoing portion of the V3 stem. In the absence of this lattice contact, the stem β-hairpin may extend farther, perhaps joining with the V3 tip to zip up much of the V3 loop.
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35. The 24-hour time point that is shown clearly depicts the protective effect of $CCR5^{2\text{-}15}$ with sCD4. $CCR5^{2\text{-}15}$ without sCD4 does not show this effect, and shorter incubations show that sCD4 enhances V3 cleavage.

36. We thank L. Chen for assistance with proteolysis of V3; S. Buchanan, D. Dimitrov, J. Hoxie, and L. Shapiro for discussions and comments on the manuscript; D. Hurt and J. Skinner for assistance with statistics; J. Stuckey for assistance with figures; and the NIH AIDS Research and Reference Reagent Program for CD4. Support for this work was provided by the Intramural Research Program (National Institute of Allergy and Infectious Diseases and National Institute of Diabetes and Digestive and Kidney Diseases) and Intramural AIDS Targeted Antiviral Program (C.A.B., P.D.K., and R.W.), by a grant from the Bill and Melinda Gates Foundation Grand Challenges in Global Heath Initiative (J.R., P.D.K., and R.W.), by the International AIDS Vaccine Initiative (J.S., I.A.W.), and by grants from NIH (J.R., J.S., and I.A.W.). This study used the high-performance computational capabilities of the Biowulf Linux cluster at NIH (http://biowulf.nih.gov). Use of insertion device 22 (Southeast Regional Collaborative Access Team) at the Advanced Photon Source was supported by the U.S. Department of Energy, Basic Energy Sciences, Office of Science, under contract W-31-109-Eng-38. Coordinates of the $CCR5^{2\text{-}15}$ NMR structure (2RLL), as well as coordinates and structure factors for the 412d-gp120-CD4 crystal structure (2QAD), have been deposited with the Protein DataBank. Coordinates of the docked CCR5 N terminus with gp120 and CD4 are available from the authors.

Supporting Online Material

www.sciencemag.org/cgi/content/full/317/5846/1930/DC1
Materials and Methods
Figs. S1 to S10
Tables S1 to S3
References

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The Slit Receptor EVA-1 Coactivates a SAX-3/Robo–Mediated Guidance Signal in *C. elegans*

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The SAX-3/roundabout (Robo) receptor has Shiga-like toxin 1 (SLT-1)/Slit–dependent and –independent functions in guiding cell and axon migrations. We identified enhancer of ventral-axon guidance defects of *unc-40* mutants (EVA-1) as a *Caenorhabditis elegans* transmembrane receptor for SLT-1. EVA-1 has two predicted galactose-binding ectodomains, acts cell-autonomously for SLT-1/Slit–dependent axon migration functions of SAX-3/Robo, binds to SLT-1 and SAX-3, colocalizes with SAX-3 on cells, and provides cell specificity to the activation of SAX-3 signaling by SLT-1. Double mutants of *eva-1* or *slt-1* with *sax-3* mutations suggest that SAX-3 can (when *slt-1* or *eva-1* function is reduced) inhibit a parallel-acting guidance mechanism, which involves UNC-40/deleted in colorectal cancer.

The UNC-6/netrin guidance cue and its neuronal receptors, UNC-5 and UNC-40/deleted in colorectal cancer (DCC), are used in different combinations to guide growing axons toward (by attraction) or away (by repulsion) from the ventral nerve cord (VNC) of *Caenorhabditis elegans* (*1*). The incomplete penetrance of pioneer-axon guidance defects observed in *unc-6/netrin* and *unc-40* single- and double-null mutants (Table 1) suggests that other mechanisms act in parallel with netrin signaling to guide axons toward the VNC. One such mechanism involves the Shiga-like toxin 1 (SLT-1)/Slit guidance cue, a large secreted protein with several predicted N- and O-glycosylation sites (*2*), and its receptor SAX-3, a homolog of the transmembrane (TM) roundabout (Robo) receptor (*3*–*6*). Both *Drosophila* and vertebrate Slit bind to Robo receptors (*3*, *7*). *C. elegans* SLT-1/Slit is expressed predominantly by dorsal body-wall muscles and repels SAX-3/Robo–expressing AVM and PVM pioneer axons toward the VNC (*2*), concomitant with UNC-40–mediated attraction of these same axons toward the VNC by ventral sources of UNC-6 (*1*).

In *C. elegans*, *slt-1* and *sax-3* mutations affect the guidance of several of the same pioneer axons (*8*). For example, the pioneer axon of the lateral AVM sensory neuron in the anterior body extends toward and then along the VNC in wild-type (WT) animals (Fig. 1, A and B), but in *slt-1* and *sax-3* mutants, the AVM axon frequently grows directly toward the head (Fig. 1C). Cell-specific rescue experiments have demonstrated that *sax-3*(+)–dependent guidance of AVM axons is cell-autonomous (*6*, *8*). Although SAX-3/Robo is the only previously known receptor for SLT-1, *slt-1* mutants of *C. elegans* do not exhibit the nerve-ring and epithelial defects of *sax-3/robo* mutants, suggesting that SAX-3/Robo has both Slit-dependent and -independent functions in development (*2*).

We identified a TM protein, enhancer of ventral-axon guidance defects of *unc-40* mutants (EVA-1), that is required to guide the AVM pioneer axon to the VNC (Fig. 1, A and B) by acting as a receptor for SLT-1. EVA-1 acts cell-autonomously, and ectopic expression of EVA-1 in SAX-3–expressing cells confers SLT-1 sensitivity to their migration. Thus, EVA-1 is predicted to be a receptor for SLT-1 that acts in conjunction with SAX-3 (as a likely co-receptor) to provide cell specificity for the activation of SAX-3 signaling by SLT-1. We also discovered a previously unknown in vivo function for SAX-3/Robo, which is to inhibit a signaling mechanism that normally functions in parallel to SLT-1 to guide pioneer axons along the dorsal/

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ventral axis. We show that this parallel-acting mechanism involves UNC-40/DCC.

AVM and PVM neurons are left, right (L/R) lineal analogs with lateral cell bodies (*9*) that extend pioneer axons along the basal surface of the epidermis toward the VNC, which they then follow toward the head (Fig. 1A). Using a *mec-7p::gfp* reporter to mark touch-receptor axons (*10*), we identified several AVM and PVM axon guidance mutants after standard ethyl methanesulfonate mutagenesis (*11*), including *eva-1(ev751)*. A predicted in-frame deletion mutant, *eva-1(tm0974)*, was provided by S. Mitani (Tokyo Women's University) (Fig. 2 and fig. S1). In *eva-1* mutants, as in *slt-1* and *sax-3* mutants, the initial pioneer phase (to the VNC) of AVM axon extension fails frequently, and axons instead grow along the lateral epidermis toward the head (Fig. 1C). Similar defects in PVM also occur in *eva-1* mutants, but at much reduced penetrance (Table 1). Both *eva-1* mutants are recessive for AVM axon guidance defects, and neither has any obvious maternal inheritance or any obvious *sax-3* mutant–like body morphology defects (*6*, *8*).

The AVM axon guidance defect in *eva-1* (*ev751*) is slightly temperature-sensitive, but deficiency heterozygotes indicate that it is null at 25°C (Table 1). *eva-1(tm0974)* causes a strong loss of function at 20° and 25°C. To eliminate EVA-1 function, *eva-1(ev751)* was used at 25°C in all experiments unless otherwise specified.

eva-1 was cloned by functional rescue with injected DNAs (Fig. 2 and table S1). Partial cDNA clones were obtained from Y. Kohara (National Institute of Genetics, Mishima, Japan). The 5′ end of the *eva-1* coding region was isolated by reverse transcription polymerase chain reaction using *SL1*- and exon-specific primers. The entire *eva-1* cDNA was sequenced and was found to encode a protein of 461 amino acid residues (fig. S1A) predicted to have a hydrophobic signal sequence for secretion (residues 1 to 23), a single TM domain, and a predicted ectodomain containing N- and C-terminal predicted lectinlike galactose (Gal)–binding domains (Fig. 2 and fig. S1B). The predicted cytodomain of EVA-1 is only 70 residues and contains a Ser/Arg–rich region (residues 400 to 412) and a single phosphotyrosine binding domain consensus binding sequence (Asn-Pro-His-Tyr). EVA-1 shares domain organization with a protein encoded within the candidate Down's syndrome region of human chromosome 21 (*12*) and also with related mammalian and nematode proteins (Fig. 2C).

In *eva-1(ev751)*, a point mutation in exon 4 changes the second conserved Cys of the second lectinlike domain to a Tyr ($Cys^{186} \rightarrow Tyr^{186}$) [supporting online material (SOM)] (fig. S1B). The *eva-1(tm0974)* allele is deleted for base pairs (bp) 5477 to 5994 in the genomic sequence of cosmid *F32A7*. Splicing around this would delete residues 111 to 223, predicting an in-frame protein of the size observed on Western blots (fig. S2).

A construct EVA-1(delC), deleted for the C-terminal 69 residues of the EVA-1 cytodomain, appears to rescue both *eva-1* alleles (Fig. 2B and table S1). This may be because the cytodomain is not required or because of complementation via multimerization of EVA-1 (delC) with either EVA-1(*ev751*) or EVA-1 (*tm0974*), both of which are predicted to have an abnormal ectodomain but a normal TM and cytodomain. Consistent with this idea, prelimi-

Table 1. Misguided AVM and PVM pioneer axons in mutant lines. % defective indicates the percentage of misguided AVM pioneer axons. SD was calculated for *N* experiments; *n*, total number of animals that were scored; ND, not determined.

Genotype	% Defective	SD	% Defective	SD	*N*(*n*)
	AVM (20 °C)			*PVM* (20 °C)	
eva-1(ev751)	42	4.8	1	0.8	7(1267)
Df(CB2772)/ev751	42	10	0	0	4(1029)
tm0974/ev751	45	12	0	0	3(357)
eva-1(tm0974)	42	8	0.4	ND	5(874)
tm0974/Df(CB2772)	50	8	0	0	7(688)
	AVM (25 °C)			*PVM* (25 °C)	
eva-1(ev751)	49	4	3	1.8	4(682)
Df(CB2772)/ev751	50	6.5	2	ND	4(454)
tm0974/ev751	38	6	0.1	ND	10(2188)
eva-1(tm0974)	38	4.5	1	0.6	3(529)
tm0974/Df(CB2772)	43	9.4	1	ND	10(2045)
unc-40(e1430)	18	2	25	3	4(626)
unc-6(ev400)	37	5.7	44	6.1	7(1231)
unc-40(e1430);unc-6(ev400)	38	3.3	37	3.4	14(1643)
eva-1(ev751)	53	8	2	1	8(3022)
unc-40(e1430)eva-1(ev751)	93	2.4	92	2.1	6(1053)
eva-1(ev751);unc-6(ev400)	93	2.8	95	6.2	8(834)
eva-1(tm0974)	43*	5.6	2	0.9	9(2031)
unc-40(e1430)eva-1(tm0974)	93	0.8	91	2.8	7(1495)
eva-1(tm0974);unc-6(ev400)	94	2.8	96	2.8	6(893)
unc-40(e1430);slt-1(eh15)	94	3.2	93	3	10(1488)
slt-1(eh15)	48*	3	2	1	10(2252)
eva-1(ev751);slt-1(eh15)	55*	2.9	5	1.7	4(2735)
eva-1(tm0974);slt-1(eh15)	42*	6.8	2	1.3	8(1704)
sax-3(ky123)	22*†	4.5	17	2.1	7(804)
sax-3(ky123)slt-1(eh15)	21*	3	18	3	4(414)
eva-1(ev751);sax-3(ky123)	19*	3.5	16	3.5	7(715)
eva-1(ev751);sax-3(ky123), slt-1(eh15)	20*	3	8	3	4(489)
eva-1(tm0974);sax-3(ky123)	25	5	17	3.9	12(1803)
sax-3(ky203)	21	3	10	3	3(293)
eva-1(ev751);sax-3(ky203)	20	3	6	3	3(531)
sax-3(ky203)slt-1(eh15)	24†	3	8	3	3(528)
unc-40(e1430)/balancer; sax-3(ky123)slt-1(eh15)	10†	3	9	2	4(423)

*A chi-square test using one degree of freedom shows that differences between *slt-1* or *eva-1* single- or double-mutant strains [that are *sax-3*(+)] and any of the *sax-3* mutant strains are highly significant ($P < 0.005$). †A chi-square test using one degree of freedom shows that the differences are highly significant ($P < 0.005$).

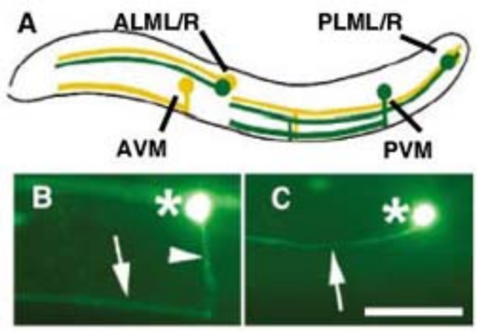

Fig. 1. AVM axon guidance defects in *eva-1* mutants. (Anterior is left in all panels.) (**A**) Representation of a lateral view of touch-receptor neurons in a WT animal. (**B** and **C**) Lateral view of AVM neurons labeled by a *mec-7p::GFP* transgene array (*10*) showing cell-body (asterisk) and axon (arrow) trajectories in a WT animal and an *eva-1* mutant, respectively. (B) In a WT animal, the AVM axon pioneers a path (region of arrowhead) from its lateral cell body (asterisk) to the VNC (arrow) before turning to grow along the VNC toward the head. (C) In an *eva-1(ev751)* mutant animal, as in *sax-3(ky123)* and *slt-1(eh15)* mutant animals, the AVM axon frequently (Table 1) grows longitudinally toward the head (arrow) without first extending to the VNC. Scale bar, 10 μm.

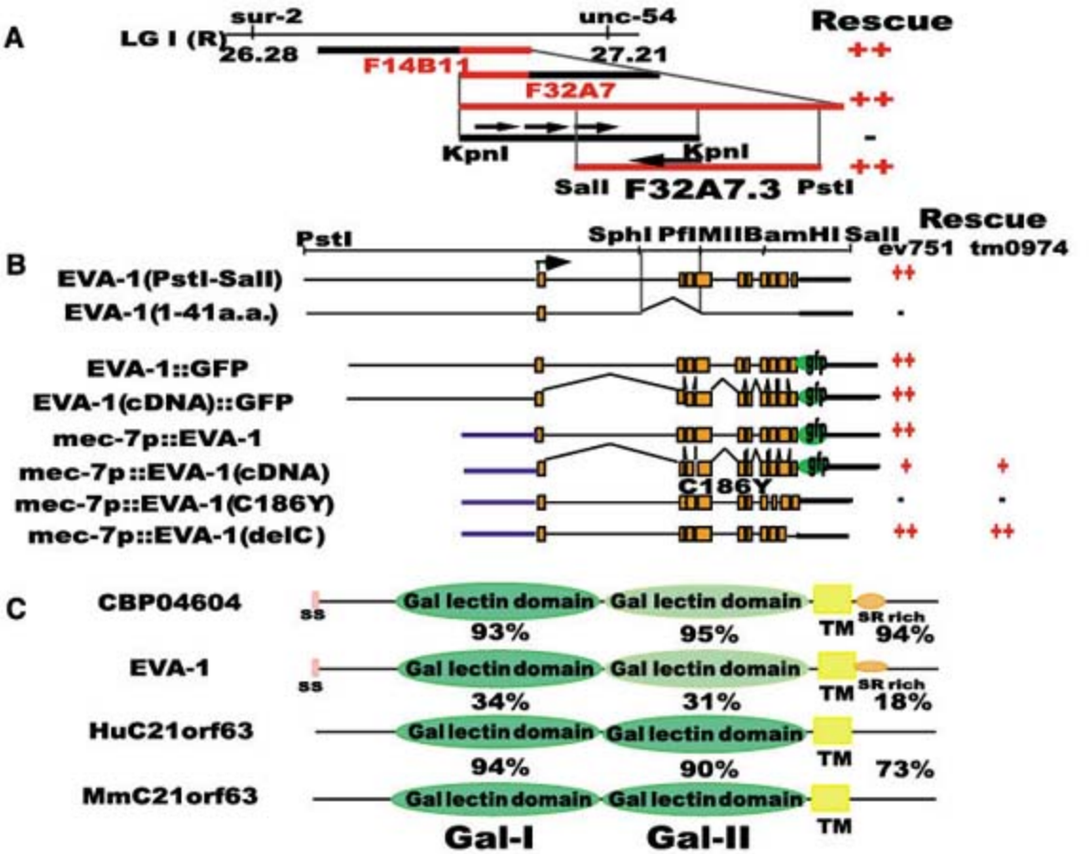

Fig. 2. Molecular characterization of *eva-1*. (**A** to **C**) DNA and cDNA sequencing methods are summarized in the SOM. (A) A subclone representing *F23A7.3a* in the overlapping region of cosmids *F14B11* and *F32A7* rescues *eva-1(ev751)* (*11*). Rescue results are shown to the right, with ++ indicating nearly full rescue). (B) *eva*-1 mutations are also rescued by various other constructs (SOM text). Exons are indicated by orange boxes, 5′ and 3′ untranslated regions are shown with thick lines, and *mec-7* promoter regions are indicated by blue lines. *eva-1(ev751)* has a missense mutation in the second conserved Cys (codon 186) in the fourth exon. A construct carrying the *ev751* mutation only slightly rescued significantly at 20°C (Table 1) but not at 25°C, indicating that the *ev751* mutation makes this protein thermolabile. (C) (Top) Nematode EVA-1 has a signal sequence for secretion (ss), two predicted Gal-binding lectin domains (green), a predicted TM domain (yellow), and predicted cytoplasmic Ser/Arg–rich domains (SR rich, orange circles). This domain organization is found in CBP04604 (*Caenorhabditis briggsae*), HuC21orf63, and MmC21orf63 [proteins identified from the Down's syndrome project (*12*)]. The numbers show the percentage identity of EVA-1 with predicted Gal-binding and intracellular domains of related proteins (see fig. S1 for direct sequence comparisons).

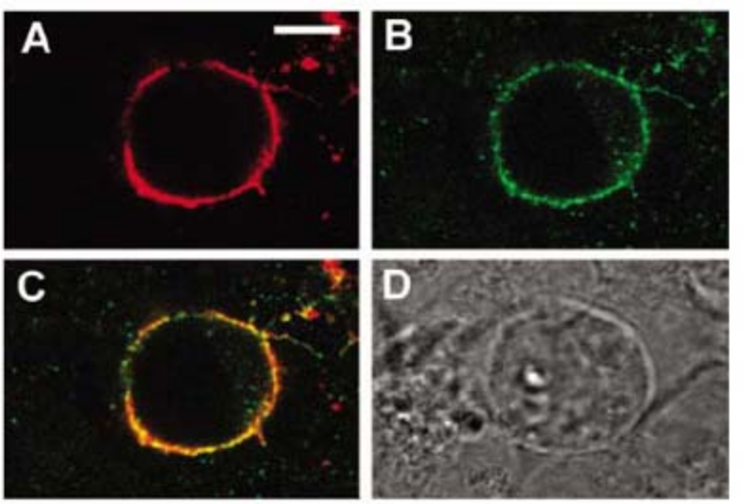

Fig. 3. EVA-1 and SAX-3 colocalization in mammalian cells. Alexa tags used for 293T cell colocalization studies were observed and photographed with a Leica SP2 confocal microscope in a single *z*-axis plane (*11*). (**A** to **D**) Confocal localization patterns of EVA-1 [secondary antibody is Alexa 488–tagged (green)] and SAX-3 [secondary antibody is Alexa 546–tagged (red)] in 293T cells are shown in (A) and (B). The overlap between Alexa 546 and Alexa 488 in (C) is yellow. (D) Differential interference contrast view of cells shown in (A) to (C). Scale bar in (A), 8 μm.

nary data indicate that EVA-1 can combine as a homomultimer (fig. S3).

AVM pioneer-axon guidance is affected by mutations in *unc-6*, *unc-40*, *slt-1*, and *sax-3* genes. To examine whether EVA-1 acts in the same pathway as UNC-6 and UNC-40, we analyzed *eva-1(ev751);unc-6(ev400)* and *unc-40 (e1430)eva-1(ev751)* double-null mutants. Their defects were either roughly equal to the additive effects of each gene (*eva-1; unc-6*) or had moderate synergistic effects (*unc-40 eva-1*) (Table 1). These results suggest that EVA-1, like SLT-1 (*2*), acts in parallel with UNC-6 and UNC-40 and somewhat redundantly with UNC-40 for AVM pioneer-axon guidance.

All or nearly all AVM pioneer-axon guidance is lost in the *eva-1(ev751); unc-6(ev400)* or *unc-40(e1430)eva-1(ev751)* double mutants, as was previously shown for *unc-40(e1430);slt-1(eh15)* (*2*). In contrast, PVM axon guidance is barely sensitive to mutations in *eva-1* or *slt-1*, but relevant double mutants suggest that SLT-1 and EVA-1 have guidance functions that are almost totally redundant with UNC-6 and UNC-40 in PVM (Table 1).

We found that AVM pioneer-axon guidance defects in *eva-1(ev751);sax-3(ky123)* and *eva-1(ev751);slt-1(eh15)* double-null and *eva-1(ev751);sax-3(ky123)slt-1(eh15)* triple-null mutants were not significantly more penetrant than the corresponding single mutants (Table 1), demonstrating that EVA-1, SLT-1, and SAX-3 all act in the same pathway for AVM axon guidance.

To examine the cell-specific expression pattern of EVA-1, we generated green fluorescent protein (GFP) transcriptional and rescuing-translational (cDNA and genomic) reporters (Fig. 2B), driven by 3.6 (first two constructs only) or 4.1 kb of *eva-1* upstream sequence and 1248 bp of endogenous 3′ genomic sequence. The translational GFP fusion protein rescued AVM (table S1) and PVM [13 out of 550 (13/550) mutant defects rescued to 0/550, respectively] and localized at or near the surface of several cell types (fig. S4F). This finding is in accordance with the predicted signal sequence and TM domain of EVA-1 (which suggests that EVA-1 is a TM protein) and is further supported by the ability of live (nonpermeabilized) EVA-1–expressing mammalian cells to bind SLT-1 (see below).

The EVA-1::GFP fusion protein is widely expressed in the developing nervous system during the period of embryogenesis (the comma stage), when most axon growth is occurring. The same result was found previously for SAX-3 (*2*). In first-larval-stage animals, strong expression is observed in ventral and dorsal nerve cords and in the PVM neurons but surprisingly not in the AVM neurons, which are more frequently misguided in *eva-1* mutants.

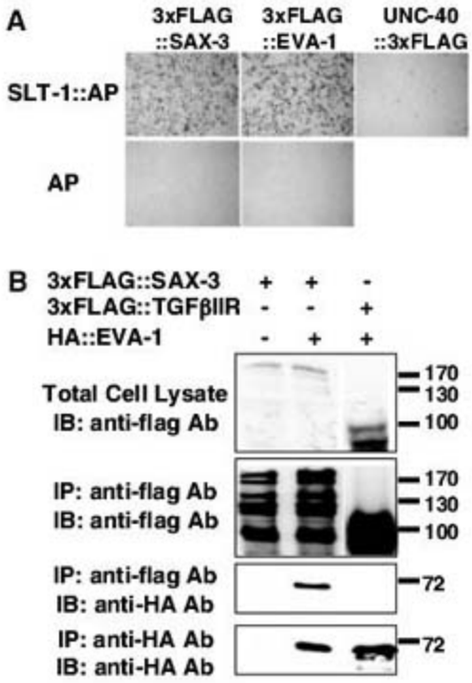

Fig. 4. Binding of EVA-1, SLT-1, and SAX-3 to each other. **(A)** 293T cells were transfected with either *3xFLAG::SAX-3–*, *3xFLAG::EVA-1–*, *UNC-40::3xFLAG–* (control at far right), *SLT-1::AP–* or *AP*-expressing plasmids. Nonpermeabilized transfected cells were incubated with SLT-1::AP or AP media (containing equal activities of AP). The FLAG-tagged proteins were expressed roughly equally, as determined by immunoblotting (fig. S7). SLT-1::AP or AP bound to the cell surface was detected by an AP color reaction (*7*). AP activity is visible on cells transfected with *3xFLAG::SAX-3* (SAX-3) or *3xFLAG::EVA-1* (EVA-1) and incubated with *SLT-1::AP*, but not on *UNC-40::3xFLAG* transfected cells incubated with *SLT-1::AP* (control at right) or on receptor transfected cells incubated with AP alone (bottom). **(B)** The cell lysates of 293T cells transiently cotransfected with *3xFLAG::SAX-3* and/or *3xFLAG::TGFbetaII receptor* (TGFβIIR) and/or *HA::EVA-1* (top) were (i) lysed and immunoblotted (IB) with anti-FLAG (total cell lysate) or (ii) immunoprecipitated (IP) with anti-FLAG (Genhunter, Nashville, Tennessee) or anti-HA, subjected to SDS–polyacrylamide gel electrophoresis, and immunoblotted with anti-FLAG or anti-HA, as shown at the left of each blot.

Table 2. ALM cell migration defects in *mec-7p::EVA-1(delC)* animals. ALM/R % anterior indicates the percentage of animals in which the final position of ALM is anterior to the WT position. SD was calculated for *N* experiments; *n*, total number of animals that were scored.

Genotype	ALM/R % anterior	SD	*N*(*n*)
mec-7p::EVA-1(delC)	13	3	3(399)
sax-3(ky123)	18	5.5	2(1669)
sax-3(ky123);mec-7p::EVA-1(delC)	15	4.4	4(447)
slt-1(eh15)	0	0.6	10(2252)
slt-1(eh15);mec-7p::EVA-1(delC)	2	1	4(751)
slt-1(eh15);sax-3(ky123)	21	1.8	7(1487)
eva-1(ev751)	0	0.6	7(894)
eva-1(ev751);sax-3(ky123)	14	2.4	4(407)
unc-6(ev400)	0	0.4	8(1231)
unc-6(ev400);mec-7p::EVA-1(delC)	18	5.1	3(366)
unc-40(e1430)	0	0.6	3(626)
unc-40(e1430);mec-7p::EVA-1(delC)	17	1.6	3(425)
myo-3p::slt-1	2	1	3(631)
mec-7p::EVA-1(delC);myo-3p::SLT-1	1	1	2(277)

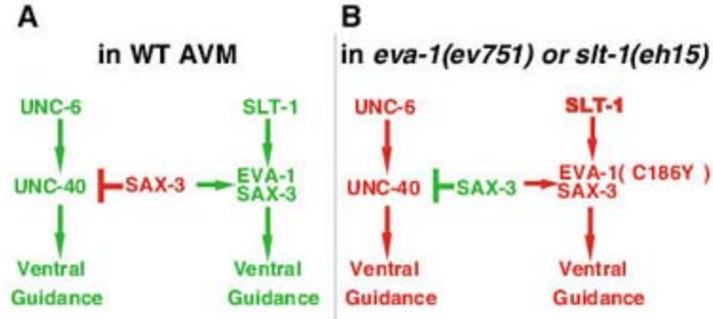

Fig. 5. A dual-function model of how SAX-3 operates in AVM ventral guidance. In AVM, UNC-6 signaling and SLT-1/EVA-1 signaling function in parallel. Green indicates functions that are active (even inhibitory functions), whereas red indicates functions that are inactive. **(A)** In WT animals, SLT-1 activation and EVA-1 expression prevent SAX-3 from inhibiting a ventral-guidance signaling mechanism involving UNC-40/DCC. Therefore, both SAX-3 and parallel signaling are fully functional for ventral guidance. **(B)** In the absence of SLT-1 or EVA-1 function, SAX-3 no longer works as a pioneer-axon guidance receptor but is freed to inhibit ventral-guidance signaling involving UNC-40/DCC. This accounts for the higher penetrance of AVM axon guidance defects in predicted *slt-1* and *eva-1* null mutants as compared with *sax-3* null mutants (Table 1).

GFP is also detected in other neurons in the head and tail and in muscle and the hypodermis, uterus, and vulva (fig. S4). Most GFP-expressing cells have no obvious defects in *eva-1* mutants but may possess signaling mechanisms that function redundantly with EVA-1, as we know to be true for PVM (Table 1).

We also examined colocalization of tagged EVA-1 and SAX-3 proteins in mammalian cells using Alexa-conjugated secondary antibodies (see SOM for procedures). The cells were visualized with goat antibody to mouse (anti-mouse) [Alexa 488 (green in Fig. 3B)] and anti-rabbit [Alexa 546 (red in Fig. 3A)] fluorescent secondary antibodies (1:250) (Molecular Probes, Invitrogen, Carlsbad, CA). Both proteins localize on or near cell membrane surfaces and in an uneven distribution that includes large regions of overlap (Fig. 3). This colocalization is consistent with the protein interaction results described below.

Cell-specific rescue and RNA interference experiments indicate that *eva-1*(+) functions in AVM for pioneer-axon guidance; however, these results are not as definitive as those of mosaic analysis (SOM text). For mosaic analysis, we made transgenic animals carrying an extrachromosomal array with both *sur-5p::SUR-5::mCherry* (to mark the nuclei of all cells carrying the transgene) and the rescuing-translational reporter in a strain carrying a genomic reporter for examining AVM axon morphology (*mec-7p::GFP*) (*10*). We then scored for loss of the *sur-5p::SUR-5::mCherry;eva-1p::EVA-1::GFP* array in cells that readily mark appropriate lineages (fig. S5). Four out of 10 losses in a progenitor to AVM had axon guidance defects, whereas 14/14 losses in other lineages had no AVM pioneer-axon guidance defects. Two out of three mosaic animals that lost the array in QR but not in its sister cell V5R had AVM axon guidance defects, whereas 6/6 losses in V5R had normal AVM axons. These results indicate that the absence of *eva-1*(+) in the descendants of QR, which include only three neurons (AVM, SDQR, and AQR) but not descendants of V5 (or other cells in these animals; fig. S5) causes AVM pioneer-axon guidance defects.

SAX-3/Robo is known to have SLT-1–dependent and –independent functions (*2*, *8*). The phenotypes and penetrance of the *eva-1* null closely mimic the *slt-1* null and also represent a fraction of *sax-3*–null mutant phenotypes and penetrance. This includes VNC midline axon crossing, nerve-ring axon guidance, CAN cell migration (*2*), viability, and body morphology and locomotion defects (*8*) (table S2). Thus, the combined data suggest that EVA-1 is required in all aspects of SLT-1–dependent but not in SLT-1–independent functions of SAX-3/Robo. Our interpretation is that there are two classes of cells that express and use SAX-3. One coexpresses EVA-1, allowing the SAX-3 receptor to

respond to SLT-1, whereas the other expresses SAX-3 but not EVA-1 and consequently does not respond to SLT-1.

If this is correct, then adding EVA-1 to SAX-3–dependent SLT-1–independent cells could make them responsive to SLT-1. We found that the expression of functional EVA-1 (delC) in the touch-receptor neurons causes ALM cell-body displacements toward the head (failure to fully migrate posteriorly), like those observed in *sax-3* but not in *slt-1* mutants (Table 2). We found that these EVA-1–induced displacements were suppressed by mutations in *slt-1*, indicating that ectopic EVA-1 made the migration of these cells dependent on SLT-1 function. Thus, EVA-1 provides the specificity needed for SLT-1 to mediate the SAX-3 signaling required to guide migrating cells and, by inference, migrating growth cones.

The simplest interpretation of our genetic results and the known domain structure of EVA-1 suggest that EVA-1 acts as a receptor for SLT-1 required for SAX-3 signaling. To further examine this possibility, we did two kinds of binding experiments (Fig. 4 legend and fig. S6). First, we found that roughly 100-fold concentrated alkaline phosphatase (AP)–tagged SLT-1 (SLT-1::AP) could bind to 293T cells expressing either SAX-3 (as expected) or EVA-1, but not to UNC-40–expressing cells (see Fig. 4A and fig. S6 for additional evidence). Similar results were obtained with the use of luminescence-based mammalian interactome (fig. S6). Second, we found that immunoprecipitation of tagged SAX-3, but not of the unrelated transforming growth factor–β type II receptor, specifically coimmunoprecipitated EVA-1 (Fig. 4B). These experiments demonstrate that SLT-1 binds to SAX-3, as expected, and also binds to EVA-1. Because EVA-1 functions in the same pathway as SLT-1, the simplest interpretation of these results is that EVA-1 binds SAX-3 as a coreceptor for SLT-1. This idea is supported by the ability of EVA-1 to provide cell specificity to the action of SLT-1 through SAX-3.

By scoring large numbers of animals grown at 25°C, we identified a previously unappreciated genetic interaction between *sax-3* and *slt-1* and a similar interaction between *sax-3* and *eva-1*. The AVM guidance defects are roughly twice as penetrant in *slt-1(eh15)* (48%) and *eva-1(ev751)* (53%) putative null alleles than in the *sax-3(ky123)* putative null (22%), suggesting that although SLT-1 and EVA-1 can function with SAX-3, they may also have an equally potent SAX-3–independent function in guiding AVM pioneer axons. However, *sax-3(ky123)slt-1(eh15)* and *eva-1(ev751); sax-3(ky123)* double mutants plus *eva-1(ev751); sax-3(ky123)slt-1(eh15)* triple mutants each show similar penetrance to the *sax-3(ky123)* single mutant (21, 19, 20, and 22%, respectively) for AVM guidance defects, suggesting that EVA-1 does not have a SAX-3–independent function (Table 1). In fact, *sax-3* mutations appear to be epistatic to the AVM axon guidance defects caused by *eva-1* and *slt-1* mutations, demonstrating that when SAX-3 is nonfunctional, ventrally oriented AVM pioneer-axon guidance is facilitated. This facilitation could occur because SAX-3, when not bound to SLT-1 or EVA-1, normally inhibits a guidance mechanism that acts in parallel to SLT-1 signaling.

Of possible relevance, it has been found for *Xenopus* neurons that netrin–UNC-40/DCC–mediated axon guidance in cultured cells can be silenced by a mechanism involving the stimulation of Robo by Slit2 and a consequent interaction between the cytodomains of Robo and DCC (*13*). These results suggest that the parallel axon guidance pathway that is inhibited by SAX-3 in *C. elegans* could be the UNC-6/netrin–UNC-40/DCC pathway. This possibility is even more enticing because *C. elegans* SAX-3 is also known to bind UNC-40, but the biological function of this interaction is unknown (*14*).

There is no obvious reason for silencing to exist in axons such as AVM pioneer axons, which would otherwise be pushed by one mechanism (SLT-1 signaling) and simultaneously pulled to the same place (the VNC) by a second mechanism (UNC-6/netrin signaling). However, it is possible that silencing is required to dampen a guidance-related signaling mechanism that would otherwise be oversaturated by a high concentration of the guidance cue. For example, as an AVM growth cone approaches the VNC, it may encounter such a high oversaturating concentration of UNC-6 that it can no longer sense the UNC-6 gradient. The reduced amount of SLT-1 near the VNC could allow SAX-3 to dampen UNC-6 signaling by binding and inhibiting an UNC-6 signaling component such as UNC-40, thereby restoring the ability of the growth cone to correctly interpret the guidance information provided near the high end of the UNC-6 gradient. If this were true, then at least some of the AVM pioneer-axon guidance defects of a *sax-3* mutant might happen because UNC-6 signaling near the VNC would not be dampened.

The above considerations raise the counterintuitive possibility that reducing UNC-40 function would suppress the AVM guidance defects of a *sax-3* mutant or a *sax-3 slt-1* double mutant. To examine this prediction, we scored AVM axon guidance defects in *unc-40/balancer;sax-3 slt-1* animals and found a significantly lower penetrance ($P < 0.005$) of AVM defects (10%) than in *sax-3* single (22%) or *sax-3 slt-1* double mutants (24%) (Table 1). This counterintuitive result is consistent with the model that SAX-3, in the absence of SLT-1 or EVA-1 function, can dampen or silence signaling through the UNC-40 receptor, which normally mediates the attraction of UNC-40–expressing axons toward ventral sources of UNC-6 (Fig. 5) (SOM text).

EVA-1 is a previously unknown receptor for SAX-3/Robo in *C. elegans* with an apparent counterpart in mammals. EVA-1 acts to allow SAX-3/Robo to elicit a guidance response to SLT-1/Slit in cells expressing both receptors. EVA-1, like SLT-1, can also regulate attractive signaling of UNC-6/netrin by dampening the signaling through UNC-40/DCC in the AVM in a manner dependent on the SAX-3/Robo cytodomain (SOM). This dampening is proposed to be a mechanism for reducing the set-point sensitivity of the AVM growth cone as it moves up the UNC-6/netrin gradient, preventing the UNC-6 signals from becoming oversaturating. EVA-1 has putative Gal-binding lectinlike domains that could bind to complex carbohydrates on SAX-3/Robo, SLT-1/Slit, or even heparan sulfate proteoglycans, which have also been shown to interact with Slit and may help to localize this secreted cue in *Drosophila* and mammals (*15*–*17*).

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Supporting Online Material

www.sciencemag.org/cgi/content/full/317/5846/1934/DC1
Materials and Methods
SOM Text
Figs. S1 to S8
Tables S1 and S2
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The Institute was established by the Austrian Government, based on a law passed by Parliament in 2006. Its funding is substantial, allowing for an approximate size of 600 employees and graduate students at the end of ten years, with significant allocations for construction, equipment and maintenance. It aims at an international mix of scientists and will choose its top researchers on the basis of their individual excellence, their scientific leadership and their potential contribution to a comprehensive research effort.

I.S.T. Austria will include a Graduate School, training scientists for the Ph.D. degree and hosting a significant number of postdoctoral fellows. While the emphasis is on basic research, applicable by-products will be exploited by licences to Industry. A nearby industrial park is being planned. The Board of Trustees (listed at **www.ist-austria.ac.at**) includes renowned international scientists and leaders of the Austrian private sector, with no political or government representatives.

The President will be the Chief Executive of I.S.T. Austria, elected by the Board of Trustees for a four year term, renewable for additional periods. Compensation will be competitive with major Research Institutes and Universities in Europe. The starting date of the appointment is negotiable.

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Confidential *applications* and *nominations* may be sent to any member of the Board of Trustees, or to **president.search@ist-austria.ac.at.** *Applications* must include CV, list of publications and a description of experience and scientific interests. *Nominations* should include an appraisal of the achievements and leadership qualifications of the nominee.

TESTING THE WATERS

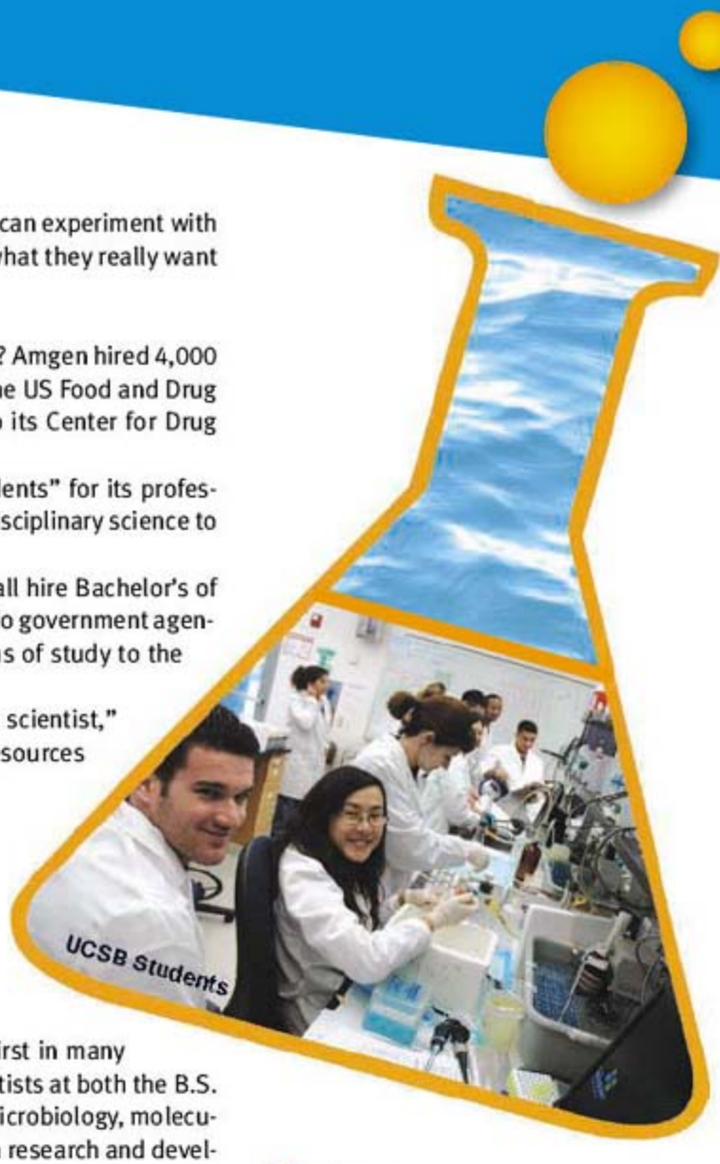
In the same period of time it takes to earn a Ph.D., budding scientists can experiment with a wide variety of educational paths and career tracks—and discover what they really want to do. **By Jill U. Adams**

Love science? Want to work in a company or a government agency? Amgen hired 4,000 people worldwide last year, a good number of them scientists. The US Food and Drug Administration (FDA) added nearly 50 new project managers to its Center for Drug Evaluation and Research (CDER) in Washington, D.C.

Want more education first? Georgia Tech seeks "Ph.D.-caliber students" for its professional Master's program, which trains them to apply innovative, interdisciplinary science to current, real-world problems.

You don't need a Ph.D. to be a scientist. Companies large and small hire Bachelor's of Science (B.S.) and Master's of Science (M.S.) scientists every year, as do government agencies and other nonprofits. Universities are noticing, tailoring programs of study to the demands of the job market.

"I always say there isn't a company out there that doesn't need a scientist," says **Rich Pennock** of Kelly Scientific Resources, a global human resources firm.



CREDIT: DR. CAROL VANDENBERG

Trends in the Marketplace

Listen to these employers from across the spectrum of employment sectors. "We are a science-led organization," says **Kathryn Carbone** of the FDA. "Amgen is a science-based company," says **Cindy Morrison.** "Science and scientists form the fundamental background of what we do at Kraft in R&D," says **Russ Moroz** of Kraft Foods.

The biotechnology and pharmaceutical industry usually pops up first in many people's minds, with companies in that sector continuing to hire scientists at both the B.S. and M.S. levels. Disciplines that are in particularly high demand are microbiology, molecular biology, and organic chemistry, with opportunities for technicians in research and development (R&D), quality control (QC), and manufacturing.

Another place to consider is the chemical industry, where there is a need for scientists in quality assurance (QA) and QC who are well versed in chemical processes.

But taking time to look beyond the obvious reveals a range of opportunities. In addition to pharmaceutical and chemical companies, commercial operations based on science include producers of cosmetics, food, and medical devices, as well as clinical research and environmental organizations.

The food industry, while not often considered by biology majors, has high demand—particularly for microbiologists—both in the R&D and QC areas, says Pennock. "If companies are producing a product for human consumption, they need to do biological testing on it—and on the equipment," he says. This is true for big companies, as well as "your small local company that makes potato chips."

The semiconductor industry and nanotechnology areas are very active, with plenty of startup companies. Government careers range from federal agencies concerned with regulatory issues, like the FDA and the US Environmental Protection Agency, to the municipality level, for example, a county interested in using geographical information systems to plot local resources.

All these organizations hire scientists at all degree levels, but that doesn't mean B.S. and M.S. scientists are just support staff for Ph.D.-level employees. In fact, a science background is valuable for a broad array of career tracks in which you can rise to the top with a Bachelor's degree.

continued »

> "I always say there isn't a company out there that doesn't need a scientist."

UPCOMING FEATURES

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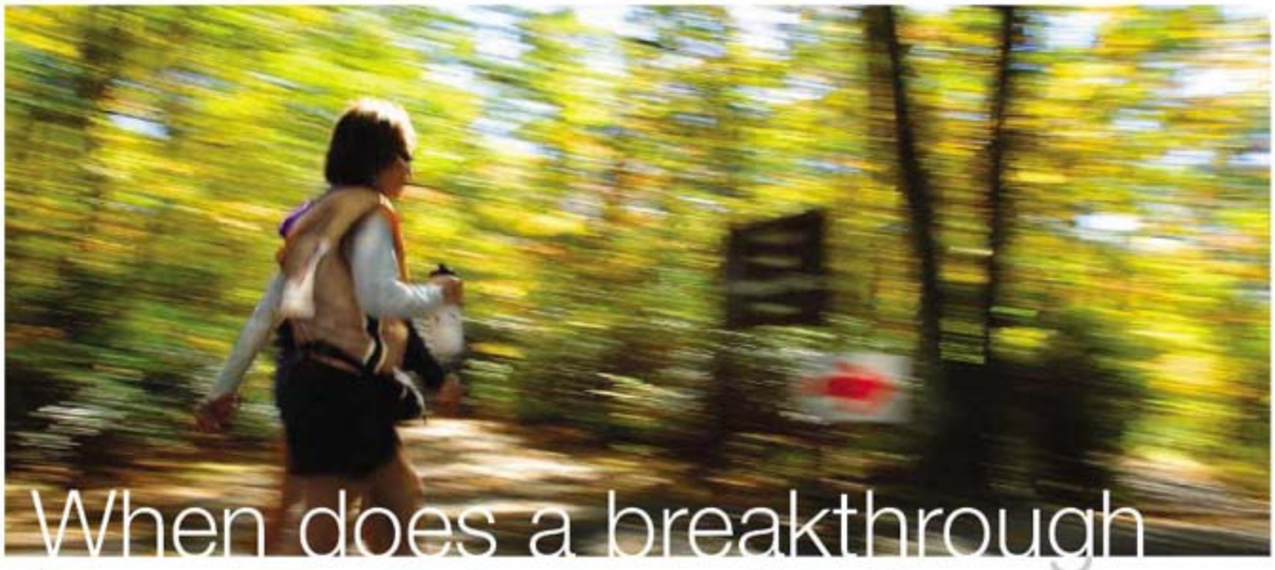

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Careers and Grad Programs for B.S./M.S. Scientists

Educational Paths

Earning a Ph.D. in science is a long road that becomes more narrow and specialized as you travel along it. For some people the time investment—six to 10 years including postdoctoral training—is worth it because they know that's what they want. However, for those less certain about forecasting their career, the shorter road to a B.S. or an M.S. degree may offer more choices and more flexibility in putting a career path together.

Don't underestimate the job market as an educational tool. Budding scientists can test-drive employment sectors, individual companies, and career tracks by taking advantage of internships and entry-level positions with on-the-job training. These experiential opportunities can help inform even the most indecisive person. And rather than shelling out for tuition, job experience as education is a paid endeavor.

Some people know early on that they want a career in science, but not necessarily to advance fundamental knowledge. They'd rather apply current knowledge to problems in society or marketplace solutions. In addition to traditional B.S. and M.S. programs, a growing trend in Master's programs is to focus on interdisciplinary fields with an applications bent.

And yet... "It's still a struggle everywhere, both on and off campus, to raise the profile of M.S. degrees," says **Jung Choi,** the director of the bioinformatics program at Georgia Tech in Atlanta, who thinks such students have much to offer. Georgia Tech is one of more than 50 institutions awarding so-called professional Master's degrees in a hundred or so, sometimes avant-garde, disciplines. In addition to bioinformatics, Georgia Tech has programs in computational finance, human-computer interactions, and prosthetics and orthotics.

"The goal is that these are all critical and strategic intellectual areas that are critical to our society," says **Bill Harbert,** co-director of the professional Master's program in geographic information systems (GIS) at the University of Pittsburgh (fondly dubbed "Pitt"). "With respect to global issues like hydrocarbon exploration, fresh water, global climate change, this is the important stuff. This is where we should be investing."

The professional Master's degree programs at Georgia Tech and Pitt are sponsored by the Alfred P. Sloan Foundation. Often compared to an M.B.A., the degree is tailored for landing a company job.

"One way the curriculum differs from a traditional discipline-based Master's is that it is interdisciplinary," says Choi. In his bioinformatics program, students take courses in math, computer science, biology, and biochemistry. They also have diverse backgrounds in terms of undergraduate study, and they learn much from each other. "They very quickly form groups, both formal and informal, where they really help each other," Choi says. "People with programming expertise will pair with people with a lot a bioscience and they work together very well."

In addition to scientific coursework, the programs include courses in law and business, which Harbert's graduates consistently say have been most useful. Another difference is that students do an internship rather than a thesis. Georgia Tech students have worked locally, at the Centers for Disease Control or Atlanta software companies, and farther afield, in Boston, Chicago, or the West Coast, says Choi.

The employability of a professional Master's degree holder is still subject to the marketplace. Choi says the demand for bioinformaticists has not been what he hoped, but blamed industry shakeups since the program launched in 2000. On the other hand, the GIS Master's students from Pitt are highly sought after. "Our best students receive two to three job offers when they're done," Harbert says, running the gamut from the major GIS software firms like Environmental Systems Research (ESRI) to the US Forest Service, from managing university GIS labs to county-level municipal jobs.

Whereas every school in the land awards Bachelor's in Science degrees each year—in standard subjects like biology, chemistry, and computer science—the University of California at Santa Barbara offers eight different specialized biology majors, including pharmacology. In fact, UCSB was first in the nation to offer an undergraduate degree in pharmacology (the program started in 1974) as a basic science—that is, not related to pharmacy training.

Abbott
www.abbott.com

Amgen
www.amgen.com

Georgia Institute of Technology
www.biology.gatech.edu/graduate-programs/bioinformatics

Kelly Scientific resources
www.kellyservices.com/web/global/services/en/pages

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University of California, Santa Barbara
www.lifesci.ucsb.edu/undergrad

University of Pittsburgh
www.pro-ms.geology.pitt.edu

US Food and Drug Administration (FDA)
www.fda.gov

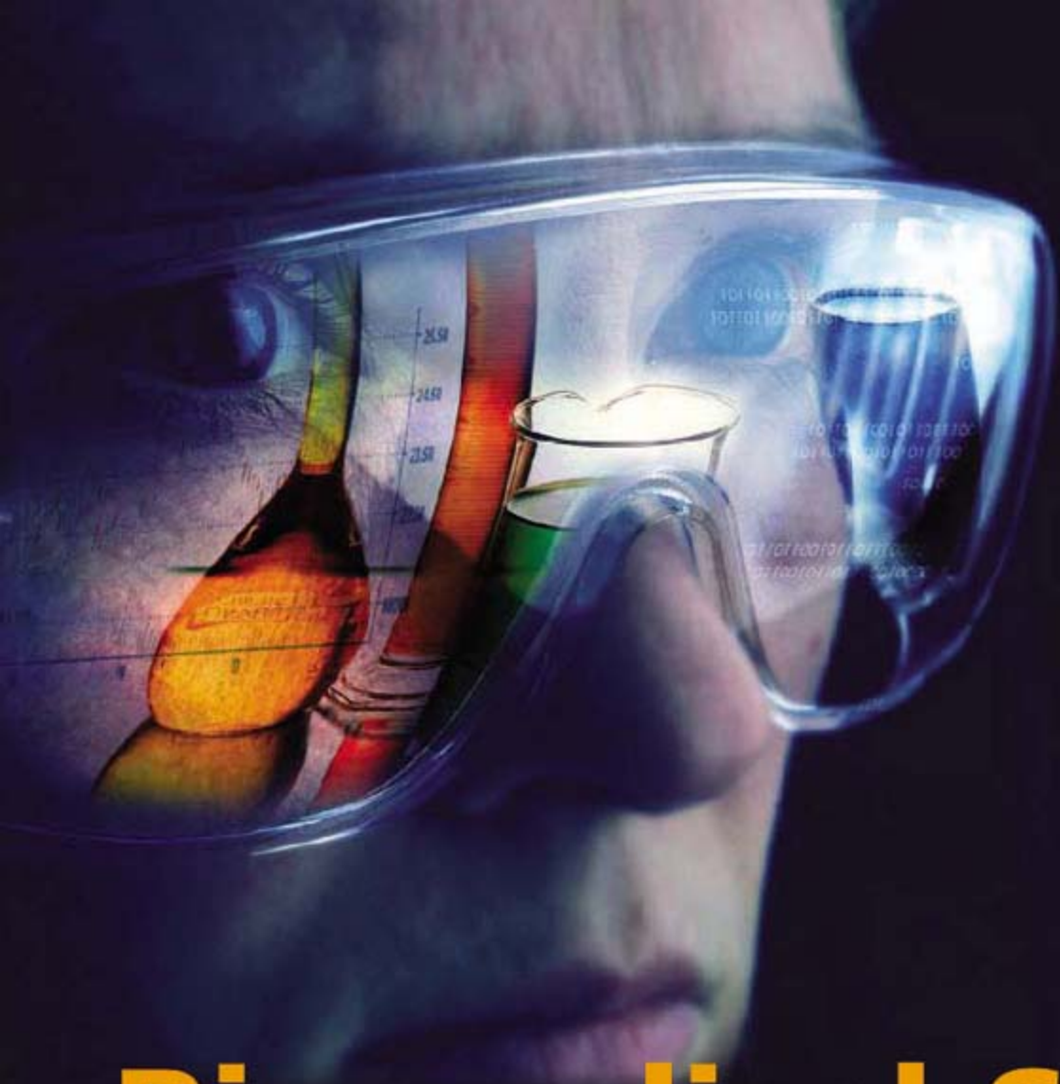
Douglas Thrower, who oversees the pharmacology major at UCSB, says, "The initial motivation was to provide students with a Bachelor's degree so they could get positions in industry directly out of school." That vision has been met with constant demand, particularly in southern California, which is dotted with biotechnology and pharmaceutical firms.

Generally students with a B.S. degree in a broad or specialized field get jobs as research assistants. "They're good stepping stone positions in that students can work their way up without getting further degrees," says Thrower.

Without a doubt, one of the choices that many B.S. and M.S. scientists take is to go back to school and get an advanced degree. The No. 1 plan for UCSB's pharmacology students is to earn a Pharm.D. and work as a pharmacist, says Thrower. Number two is medical school. Likewise, a quarter of the students that Choi has tracked have gone on to Ph.D. programs.

Career Ladder

Kraft Foods employs a variety of scientists (and engineers), continued »



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Careers and Grad Programs for B.S./M.S. Scientists

"It's not uncommon to hire a Bachelor's graduate who has had a few years of experience. Those folks are able to hit the ground running."
–Jim Summers

says Moroz, a vice president of global technology and quality at the company. Scientists work in the development of products, packaging, and processes and they work in basic research to explore the chemistry of flavors, the physiology of taste, and nutrition of novel ingredients. Kraft has four major research and development sites in the United States: in New Jersey, New York, Wisconsin, and Illinois.

Amgen values science degrees across the company, says Morrison, including project management, clinical research, licensing and business development, and marketing. Company sites are located in California, Washington, and Massachusetts.

For research positions, there's no substitute for laboratory experience, says **Jim Summers,** vice president of advanced technologies at Abbott, which has research sites in Illinois, New Jersey, Massachusetts, and Germany. That means M.S. scientists, with more time at the bench, have an advantage over B.S. candidates. To Summers, it represents a certain level of intellectual maturity. "It's people who have tackled a research problem from a problem-solving point of view as opposed to simply following a procedure," he says.

At the same time, "it's not uncommon to hire a Bachelor's graduate who has had a few years of experience," says Summers. "Those folks are able to hit the ground running and are able to take on the kinds of problems that we would typically have for them."

Laboratory experience is very important on an applicant's resume, says Moroz, "even if the person's not going to be doing what you would view as a classical lab type job." He sees hands-on experimental work as good practice in connecting theory to application. In the workplace, "it's all about how you solve the problem," he says. "Most of what we work on, in one form or another, are problems."

Employers also value evidence of "soft skills" on a resume: leadership, teamwork, and communication. "A team environment—it almost sounds trite, because you hear it more and more in business," says Pennock of Kelly Services, "but it's even more important in the science world as scientific disciplines are starting to cross."

Kraft is a company that represents the breadth of opportunities for scientists, from basic research and quality control to regulatory affairs and management. And yet, the most specialized scientists doing the most fundamental research are likely to be Ph.D.s. Other companies, like the entrepreneurial biotechnology giant Amgen and the century-old pharmaceutical company Abbott, pride themselves on having no glass ceiling for those without a doctorate.

With good performance and accumulated skills, B.S. or M.S. scientists can be promoted into positions to which a Ph.D. with postdoctoral experience would be hired, says Morrison, vice president of human resources for research and development at Amgen. "We have several examples of that," says Morrison. "One of our vice presidents of research does not have a Ph.D." Similarly at Abbott, both B.S. and M.S. scientists are members of the company's scientific honorary society, "which is recognized as the very top tier of scientists in the organization," Summers says.

On-the-Job Education

Kraft, Amgen, and Abbott all have active summer internship programs for students from undergraduate to doctoral. In addition to making connections and gaining on-the-job experience, interns benefit from the same evaluation and development plans that employees do. By mapping out plans with their supervisors, students can learn what is required for different career tracks, including what they need to do to get there.

Large corporations typically offer job-related training and encourage employees to move among different company divisions. Many have tuition reimbursement plans for those who wish to pursue further university education. Abbott has a formal program for B.S. scientists to obtain their Master's degrees in night school.

In other situations, employees receive specific training for a particular job. Regulatory affairs is the name of the game at the FDA, in Washington, D.C., and the specialized aspect of reviewing and evaluating drugs or vaccines means there's significant training after hire, says **Kathryn Carbone,** associate director for research at the Center for Biologics Evaluation and Research (CBER). "This is one of the few places where you can get training in regulatory oversight within a research environment," Carbone says. And it's critical, she says, because "we have an enormous public health responsibility."

Over at the FDA's CDER, B.S. and M.S. graduates are hired as regulatory project managers for new drug applications. In addition to a science degree, the best recruits have some project management work experience, but laboratory experience is not that important, says **Eldridge Coles,** head of recruitment for the Office of New Drugs (OND). Analytical skills and communication skills, however, are key.

"Project managers play an important role in shepherding an application through the review process," Coles says, which requires coordinating with the FDA's multidisciplinary teams of scientific and medical reviewers and liaising with their industry counterparts. Each project manager is assigned a mentor to help get through the first year of intensive training and to provide advice on the responsibilities of the position.

Coles says the CDER is constantly looking to hire well-qualified candidates to fill its project management ranks. "It can be a very challenging and demanding job," says Coles, who acknowledges the position has one of the OND's higher turnover rates. For many, the demands are offset by the rewards of the work itself, not to mention the competitive benefits and salaries that government offers. Others take advantage of the on-the-job training and translate it into new opportunities—with several years experience, FDA project managers are highly sought after by industry.

Still not sure what you want to do? Realize that a wide variety of companies and organizations are built upon scientific foundations. Consider something off the beaten track, try stuff out, and start educating yourself with experience.

Jill Adams is a freelance writer living in upstate New York.

DOI: 10.1126/science.opms.r0700040

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UBC Prof. Brett Finlay and PhD student Jennifer Bishop from Barrington, RI, USA.

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Contact: Janeen Greene, gradbio@neu.edu

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Contact: Robert Schatz, Graduate Program Director, r.schatz@neu.edu.

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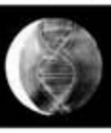

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R&D Scientist, Bioinformaticist – PhD in Molecular/Cellular Biology plus MS or equivalent in Computer Science. Provides support for research in biotechnology: designs experiments, develops new bioinformatics tools, and executes new strategies for data analysis and interpretation. (RND00001062)

R&D Researcher, Bioinformaticist – Master's Degree in Computer Science with experience in Biology. Provides support for research in biotechnology by developing, implementing, and applying new bioinformatics tools and databases. (RND00001171)

R&D Scientist, Statistician – Master's Degree in Statistics, Biostatistics or Mathematics preferred. Collaborates with the biotechnology team to develop statistical tools, and implement new methods for analysis of experiments. (RND00001028)

R&D Researcher, Statistical Analyst/Programmer – Bachelor's in Statistics, Biostatistics or Mathematics preferred. Supports Statistician in the roles described above on various projects in the bioinformatics area. (RND00001124)

For more job details and to apply online **(refer to appropriate Job Code listed with description above)** go to:

www.usjobs.pg.com

The preferred candidate would be a U.S. citizen or national, refugee, asylee or lawful permanent resident. We will consider exceptional candidates who do not meet these restrictions.

No agency referrals.
An Equal Opportunity Employer.

KU THE UNIVERSITY OF KANSAS

Graduate Program in Molecular Biosciences

Outstanding graduate training is offered in six focus areas:

- **Biochemistry and Biophysics**
- **Bioinformatics**
- **Genetics**
- **Microbiology**
- **Molecular, Cellular, and Developmental Biology**
- **Neurobiology**

The program provides support for all graduate students, including a competitive 12-month stipend plus tuition.

For a full description of our program, faculty research interests and admission requirements visit **www.molecularbiosciences.ku.edu**.

Research Staff Opportunities – St. Jude Children's Research Hospital

St. Jude Children's Research Hospital is recognized as one of the premier centers for the research and treatment of childhood catastrophic diseases.

New and exciting research positions are available in our academic departments. Entry-level positions are available, with opportunities for advancement within the hospital's research career ladder.

At the entry level, a bachelor's or master's degree in an appropriate scientific field with no additional experience is required. For specific job requirements, visit our Web site, www.stjude.org/jobs.

St. Jude Children's Research Hospital
ALSAC · Danny Thomas, Founder
Finding cures. Saving children.

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Ranked No. 1 in the "Best Places to Work in Academia" by* The Scientist *magazine for 2006

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M.D./Ph.D. Scholars Program
Educating the Physician-Scientists of Tomorrow
Phone: (402) 559-8242
Toll-free: (800) 642-1095
Fax: (402) 559-6002
Web: www.unmc.edu/mdphd

University of Nebraska Medical Center

WAYNE STATE UNIVERSITY

Biology Faculty Positions

The Department of Biological Sciences at Wayne State University anticipates four tenure-track openings for new faculty. Rank will be dependent upon qualifications. Preference will be given to candidates who use state-of-the-art approaches to study complex biological problems that complement existing research programs.

Cell Biologist: Areas of interest include, but are not limited to, neurobiology, lipids and signal transduction, RNA biology, and organelle biogenesis and function.

Developmental Biologist: We are particularly interested in individuals taking a systems approach to the analysis of developmental problems, including but not limited to epigenetics and developmental plasticity, gastrulation/neurulation in a vertebrate model system, and plant development.

Ecologist: Areas of interest include, but are not limited to, urban or aquatic biology, with a focus at any level of biological organization (population, community, or ecosystem).

Microbiologist: Areas of interest include, but are not limited to, immunology of infectious diseases, host-pathogen interactions, and infectious disease processes.

Wayne State University is a large, comprehensive, nationally ranked research institution that offers generous start-up packages. Applicants must have a Ph.D. degree, postdoctoral experience and an outstanding record of research achievement. Successful applicants are expected to establish and maintain vigorous, externally funded research programs and participate in graduate and undergraduate education. All positions will officially be posted on-line at **jobs.wayne.edu** in early October. Only those application materials that are submitted to this site will be considered. In addition to their online application that includes cover letter and curriculum vitae, applicants must submit a 2-page statement of research plans, a 1-page statement of teaching interests and philosophy, and have three letters of reference sent to: **Chair, Faculty Search Committee, Department of Biological Sciences, Wayne State University, 5047 Gullen Mall, Detroit, MI 48202**. Review of applications will begin immediately and the search will remain open until the positions have been filled. Applications will be considered only when all materials have been received.

Wayne State University is an Affirmative Action/Equal Opportunity Employer.
Women and members of minority groups are especially encouraged to apply.

Endowed Professorship for Dementia Research

The Department of Neurology and the Neuroscience Center at the University of North Carolina School of Medicine are seeking candidates with an interest in degenerative neurological diseases that produce cognitive impairment for appointment to full professor on the tenure track. The qualified candidate will have an M.D. or M.D./Ph.D. and an established record of excellence in research as reflected by peer-reviewed publications and independent external funding. He/she will be expected to conduct a laboratory-based research program investigating mechanisms of cellular death and dysfunction in neurodegenerative diseases using state-of-the-art cellular and molecular techniques. The position includes an endowed professorship of $1 million, ample modern laboratory space in the UNC Neuroscience Center and a generous start-up package. The UNC Neuroscience Center maintains outstanding Core Facilities that support confocal and multiphoton imaging, vector construction and ES cell electroporation for generation of mouse genetic models, and Affymetrix GeneChip technology for expression profiling and SNP analysis.

Interested candidates should contact: **William J. Powers, MD, H. Houston Merritt Professor and Chair, Department of Neurology, 3114 Bioinformatics Building CB 7025, University of North Carolina School of Medicine, Chapel Hill, NC 27599-7025; (919) 966-8178; holzmachere@neurology.unc.edu.**

EOE

DANA-FARBER CANCER INSTITUTE

Dedicated to Discovery...Committed to Care.

ASSISTANT PROFESSOR

Tenure Track

Systems Biology/Genetics

The Department of Cancer Biology at the Dana-Farber and the Department of Genetics at Harvard Medical School seek well-qualified applicants for a tenure-track position at the Assistant or Associate Professor level to serve in a new Center for Cancer Systems Biology (http://ccsb.dfci.harvard.edu). The successful candidate is expected to direct innovative and independent research and to participate in the teaching activities of the Department of Genetics. Candidates combining systems biology and genetics to investigate normal biological processes and/or human diseases, particularly cancer, are encouraged to apply. CCSB provides a highly integrative and collaborative environment to develop interdependent systems biology research programs. An attractive start-up support package is provided which includes laboratory space in the new Smith Research Building of the Dana-Farber Cancer Institute. The successful candidate will also be a full member and active participant in the Department of Genetics (http://genetics.med.harvard.edu). Applicants must hold a Ph.D, M.D./Ph.D. or M.D. degree, have completed post doctoral training, and have a strong record of research accomplishments.

Applicants should submit electronic (pdf) copies of curriculum vitae, bibliography, a description of research accomplishments and future research interests (limit to two pages) by December 30, 2007, and ask four references to provide letters of recommendation. These materials should be sent to the following email address:

Deborah_goff@dfci.harvard.edu

HARVARD MEDICAL SCHOOL

Applications must be received by December 30, 2007

The Dana-Farber Cancer Institute is an Equal Opportunity Employer. Applications from women and minorities are encouraged.

SHARE THE VISION. FIND THE CURE

Program Director – Undergraduate Science Education

The **Howard Hughes Medical Institute**, a leading philanthropy devoted to biomedical research and science education, is seeking a Program Director to join our headquarters in **Chevy Chase, MD**.

The Program Director, with an annual budget of over $40 million, oversees HHMI's Undergraduate Science Education activities, including institutional grants to colleges and research universities, and individual grants to professors.

The successful candidate will have an advanced degree in science, a national reputation in science undergraduate education, demonstrated skill in managing people and programs, and a commitment to building innovative programs to strengthen biomedical science education.

Responses should include research and undergraduate science education accomplishments, a description of administrative and management experience, and a statement of vision of science education challenges and opportunities.

Visit **www.hhmi.org** for a complete position description.

Send CV and cover letter to:
Program Director
Howard Hughes Medical Institute
c/o PRM Consulting, Inc.
Attention: Gregory Davis, Managing Director
1814 13th Street, NW Washington, DC 20009

The Howard Hughes Medical Institute is an Equal Opportunity Employer

HHMI
HOWARD HUGHES MEDICAL INSTITUTE

THE CHINESE UNIVERSITY OF HONG KONG

Applications are invited for:-

School of Pharmacy

(1) Associate Professor / Assistant Professor

(Ref. 07/207(665)/2)

Applicants should have (i) a PhD degree in pharmacokinetics/quantitative pharmacology or equivalent; and preferably (ii) postdoctoral training as well as experience in genomics, biomarkers, and/or bioinformatics. The appointee will (a) participate in teaching at postgraduate and professional levels; and (b) develop an outstanding independent research programme that will bridge basic research in modern drug design and delivery as well as clinical research in oncology, diabetes, digestive disease and infectious disease. Collaborative research with other institutions is encouraged. Appointment will normally be made on contract basis for up to three years initially commencing January 2008, leading to longer-term appointment or substantiation later subject to mutual agreement. Further information about the School is available at *http://www.pharmacy.cuhk.edu.hk*. For enquiries, please contact Professor Ho Yee Ping (E-mail: *yeepingho@cuhk.edu.hk*). Applications will be accepted until the post is filled.

(2) Associate Professor / Assistant Professor

(Ref. 07/208(665)/2)

Applicants should have (i) a PhD degree in translational research or equivalent; and preferably (ii) postdoctoral training as well as experience in nanomedicine, nanotechnology, tissue engineering, or stem cell research. The appointee will (a) participate in teaching at postgraduate and professional levels; and (b) develop an outstanding independent research programme that will complement existing strengths in biopharmaceutics of traditional Chinese medicine, modern drug delivery, drug design and drug formulation engineering. Collaborative research with other institutions is encouraged. Appointment will normally be made on contract basis for up to three years initially commencing in 2008, leading to longer-term appointment or substantiation later subject to mutual agreement. Further information about the School is available at *http://www.pharmacy.cuhk.edu.hk*. For enquiries, please contact Professor Ho Yee Ping (E-mail: *yeepingho@cuhk.edu.hk*). Applications will be accepted until the post is filled.

Salary and Fringe Benefits

Salary will be highly competitive, commensurate with qualifications and experience. The University offers a comprehensive fringe benefit package, including medical care, plus a contract-end gratuity for appointments of two years or longer, and housing benefits for eligible appointees.

Further information about the University and the general terms of service for appointments is available at *http://www.cuhk.edu.hk/personnel*. The terms mentioned herein are for reference only and are subject to revision by the University.

Application Procedure

Please send full resume, copies of academic credentials, a publication list and/or abstracts of selected published papers, together with names, addresses and fax numbers/e-mail addresses of three referees to whom the applicants' consent has been given for their providing references (unless otherwise specified), to the Personnel Office, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong (Fax: (852) 2603 6852) by the closing date. The Personal Information Collection Statement will be provided upon request. Please quote the reference number and mark 'Application - Confidential' on cover.

CELL BIOLOGY

The Department of Biology at American University invites applications for a **TENURE TRACK** position at the Assistant Professor level to begin in Fall 2008. A Ph.D. in Cell Biology or closely related field, an established record or outstanding potential for research, and teaching experience are required. Responsibilities include teaching cell biology with laboratory plus additional biology courses for majors and non-majors, developing a strong research program, supervising undergraduate and graduate student research, and providing university service.

Submit a letter of application, curriculum vitae, brief summary of research plan, and statement of teaching philosophy and have three letters of reference sent directly from the referees to: **Dr. Schaeff, Cell Biology Search Committee Chair, Department of Biology, American University, 4400 Massachusetts Avenue, N.W., Washington, D.C. 20016-8007, USA**; electronic submissions: **biology@american.edu**, pls use **"Cell Biology Search"** as your subject line. Review of applications will begin on **November 1, 2007** and continue until the position is filled. American University is seeking highly dedicated teachers and scholars who are deeply committed to interdisciplinary learning, the application of new technologies in teaching and scholarship, and to the preparation of students for life in a diverse and rapidly changing global society.

American University is an Affirmative Action Equal Opportunity Employer, committed to a diverse faculty, staff and student body. Women and minority candidates are strongly encouraged to apply.

VirginiaTech

Invent the Future

Cluster Hires

College of Science

COLLEGE OF SCIENCE
BIOLOGICAL SCIENCES • CHEMISTRY
• ECONOMICS • GEOSCIENCES • MATHEMATICS
• PHYSICS • PSYCHOLOGY • STATISTICS

The College of Science at Virginia Tech, in support of the university's strategic plan, is expanding its research presence in two broad areas: **Energy and the Environment** and **Health, Food, and Nutrition.** Faculty members will be recruited across several colleges to promote research efforts in these areas. We intend to recruit 10 or more new faculty in disciplines within the College of Science.

Both junior and senior level candidates are encouraged to apply. Please visit **www.cos.vt.edu** and click on the links under Job Openings. Consideration of applications will begin as early as **November 1, 2007** and will continue until the positions are filled.

Virginia Tech is an AA/EEO Employer; applications from members of underrepresented groups are especially encouraged.

UNSW

THE UNIVERSITY OF NEW SOUTH WALES

Professor of Synthetic Chemistry

FACULTY OF SCIENCE
School of Chemistry
REF. 5301

The School of Chemistry is committed to providing a stimulating research environment that promotes excellence and innovation in chemical research. We are seeking to appoint an exceptional individual who will strengthen this environment, by providing academic leadership and contributing with vision and innovation in the area of Synthetic Chemistry.

Teaching approximately 2000 undergraduate students per year, Academics in the School contribute to teaching in many Science programs, including the BSc, the BSc in Nanotechnology, and BSc in Food Science. The successful applicant will be expected to establish a prosperous, self-funding research group that carries out cutting edge experimental research in the area of synthetic chemistry with a preferred emphasis on bioactive molecules.

This is a full time position. The current salary for Professor is AUD$130,147 per year. Membership of an approved University superannuation scheme is a condition of employment for this position.

Women and EEO groups are encouraged to apply. The University reserves the right to fill the position by invitation or not to fill the position.

Applicants should systematically address the selection criteria in their application.

Enquiries regarding this position should be directed to Associate Professor Barbara Messerle, Head of the School of Chemistry at: b.messerle@unsw.edu.au

EOWA EMPLOYER OF CHOICE FOR WOMEN

Applications close: 26 October 2007

For full details of this and other vacancies check our website at
www.hr.unsw.edu.au/jobs.html

Johns Hopkins Medical Institutions Tenure-Track Positions

Influenza and Respiratory Virus Translational Research

Human Immunology, Vaccinology, Pharmacology

The Division of Infectious Diseases of the Johns Hopkins School of Medicine is recruiting 1-2 faculty at the Assistant or Associate Professor level to contribute to an emerging institutional Respiratory Viruses Program. Our focus is on persons with proven capabilities to conduct independent research on respiratory infections, especially investigations that contribute to the prevention or treatment of influenza in humans. This recruitment contributes to expanding programs in influenza virology, structural biology, and vaccine testing. Emphasis will be given to researchers with complementary research such as in molecular biology of viral replication, host virus interactions, and quantitative analysis of viral dynamics.

Candidates must have earned an MD and/or PhD degree and have a record of acquiring research funding and producing outstanding scholarship. Salary and resources will match experience.

Candidates should provide a curriculum vitae, a one-page statement of career interest, and 3 professional references to: **Dr. David Thomas, Chief Infectious Diseases, Johns Hopkins School of Medicine, Suite 437 1830 Monument Street, Baltimore, Maryland 21205** or by email care of Nadia Hay **nhay@jhmi.edu**. Application review will begin in Fall 2007.

Johns Hopkins is an Equal Opportunity Employer.

STANFORD UNIVERSITY DEPARTMENT OF CHEMICAL AND SYSTEMS BIOLOGY

The Department of Chemical and Systems Biology at Stanford University School of Medicine invites applications for a tenure-track or tenured position at the **ASSISTANT or ASSOCIATE PROFESSOR** level. We are particularly interested in candidates who have research interests at the interface of biomedical and physical sciences (e.g., chemical biology, quantitative biology, systems biology). Candidates could focus on either specific methodologies (e.g. mass spectroscopic approaches to proteomics) or specific biological problems where chemical and systems-level approaches are particularly well-suited. However, outstanding applicants in any area of signal transduction or cellular regulation are welcome. Stanford offers an outstanding environment for creative interdisciplinary biomedical research. Rank and salary are dependent on the candidate's qualifications. The predominant criterion for appointment in the University Tenure Line is a major commitment to research and teaching.

Candidates should have a Ph.D. and/or M.D. degree and postdoctoral research experience. Stanford University is an equal opportunity employer and is committed to increasing the diversity of its faculty. It welcomes nominations of and applicants from women and minority groups, as well as others who would bring additional dimensions to the university's research, teaching, and clinical missions. Candidates should send curriculum vitae, a description of future research plans and the names of three potential referees by November 16 to:

James Ferrell, Professor and Chair
c/o Jean Kavanagh, FAA
Department of Chemical and Systems Biology
269 Campus Drive, CCSR Bldg Room 3145A
Stanford University School of Medicine
Stanford CA 94305-5174

University of California -- Santa Barbara
Dean of Mathematical, Life, and Physical Sciences
Susan and Bruce Worster Dean of Science

The University of California, Santa Barbara (UCSB) invites nominations and applications for the position of Dean of Mathematical, Life, and Physical Sciences and Susan and Bruce Worster Dean of Science. We seek an individual with an outstanding record of scholarly achievement commensurate with a professorial appointment in the appropriate department, demonstrable vision and creative leadership abilities, documented credentials in administration, a commitment to enhancing the diversity of the university community, and an established national and international reputation within the broader scientific community. The successful applicant will be expected to provide direction, inspiration, and the administrative ability to guide and further develop the size and stature of Mathematical, Life, and Physical Science academic programs. In addition to these attributes, important qualifications include a broad appreciation and perspective for all fields of the mathematical, life, and physical sciences, strong support for and facilitation of multi- and inter-disciplinary research endeavors, and a demonstrated ability to interact effectively with industrial, governmental, and educational institutions, as well as philanthropic Foundations.

UCSB is a young, vibrant Research I university of 20,000 students, located in a spectacular natural seaside setting. The Division of Mathematical, Life and Physical Sciences (MLPS) is one of three divisions within UCSB's College of Letters and Science. MLPS includes 13 academic departments and programs: Biomolecular Science and Engineering; Chemistry and Biochemistry; Ecology, Evolution and Marine Biology; Environmental Studies; Geography; Earth Science; Marine Science; Mathematics; Molecular, Cellular and Developmental Biology; Physics; Psychology; Speech and Hearing Sciences; and Statistics and Applied Probability. The 282 faculty members include three Nobel laureates, fourteen members of the National Academy of Sciences, one member of the Institute of Medicine, and many PECASE, NSF CAREER, Packard, Guggenheim, and Sloan Fellowship awardees. Total annual extramural funding for research in MLPS was approximately $83 million in 2006-2007. Within the division there currently are 729 doctoral and masters students, 4682 undergraduate students and approximately 200 post doctoral fellows mentored by MLPS faculty.

The MLPS Dean's purview includes numerous facilities and interdisciplinary centers with diverse missions ranging over bio-medical imaging, geographical analysis, environmental biodiversity, organic solids, biochemistry, biomedical research, virtual environments and financial mathematics and statistics. In addition, MLPS faculty lead important federally funded research centers; among them the Kavli Institute for Theoretical Physics, the National Center for Ecological Analysis and Synthesis, the Institute for Collaborative Biotechnologies, the Marine Science Institute, and the Southern California Earthquake Center.

All inquiries, nominations and applications will be held in strictest confidence. Applications should include a letter of interest and a curriculum vitae. Applications and nominations will be received until the position has been filled. The screening process however, will begin immediately, and applications are encouraged prior to **November 30, 2007**. Nominations and expressions of interest should be submitted to:

Professors James Allen and Diane Mackie
Chairs, Search Committee for the Dean of Mathematical, Life, and Physical Sciences
C/o Kathy Upton, Office of Academic Personnel, Cheadle Hall 4105, Mail Code 2034
University of California
Santa Barbara, CA 93106-2034

UCSB is an Equal Opportunity and Affirmative Action Employer and Educator.

Research Scientist, MDI Biological Lab

The Mount Desert Island Biological Laboratory (MDIBL), located on Mount Desert Island, Maine, home of Acadia National park, is a 109-year-old independent marine and biomedical research institution and an international center for comparative physiology, toxicology and marine functional genomic studies.

MDIBL invites applications for a junior level research position (equivalent to Assistant Professor) in developmental biology, cell biology, physiology, toxicology, or bioinformatics. Within the chosen research area there should be an emphasis on comparative functional genomics and marine model systems.

Candidates must possess a PhD or MD. A strong record of continuous research productivity and clearly demonstrated potential for funding is required. This appointment is for a minimum of three years. Interest in collaboration with other scientists at MDIBL is essential. Salary, start-up resources and laboratory space are competitive and commensurate with experience.

Send cover letter, vitae, research plans, names and addresses of three references to **Dr. Patricia Hand, Administrative Director, MDI Biological Laboratory, Box 35, Old Bar Harbor Rd., Salisbury Cove, ME 04672.** Address electronic applications to phand@mdibl.org. Review of applications will begin November 1st and continue until the position is filled.

MDI Biological Lab

MDIBL is an Affirmative Action/Equal Opportunity Employer.
Women and members of minority groups are encouraged to apply.

UNIVERSITY OF MARYLAND

ASSISTANT/ASSOCIATE PROFESSORS, Tenure/Tenure Track Faculty - The University of Maryland, Department of Plant Science and Landscape Architecture seeks candidates for Two (2) tenure-track faculty positions at the Assistant or Associate Professor level. One position is a 12-month tenure-track appointment with a research focus on woody plant pathology and having duties split 58% research and 42% teaching. This position offers a unique opportunity to build upon a developing Plant Protection Center Initiative involving the College, USDA-APHIS and MDA in the training of future plant protection professionals. The second position is a 9-month tenure-track appointment with duties split 85% research and 15% teaching in the area of plant genetics, functional genomics and/or molecular physiology. Each position offers opportunities to interact with University of Maryland faculty affiliated with the College of Agriculture and Natural Resources, the College of Chemical and Life Sciences, the University of Maryland Biotechnology Institute, as well as scientists at USDA, FDA, EPA, and NIH. PhD degree in a closely related discipline required. A detailed position description for each position can be found at **http://www.agnr.umd.edu/jobs/agnrjobs/home.html**. Salary will be commensurate with experience.

College Park is the flagship campus of the University System of Maryland with over 2,800 faculty and 25,000 undergraduate and 10,000 graduate students. The University of Maryland offers an extensive benefits package. Candidates should submit: a letter of application; a complete signed CV; transcripts (copy acceptable for application process); and the names, addresses, telephone numbers, and email addresses of 3 professional references to: **Susan Klotz, Department of Plant Science and Landscape Architecture, 2102 Plant Science Building, University of Maryland, College Park, MD 20742** (email: **sklotz@umd.edu**). Applicants at the Associate Professor level should include copies of three representative publications. Review of application materials will begin **November 1, 2007**. However, the search will continue until the positions are filled.

EEO/AA

MAYO CLINIC

FACULTY POSITION IN CANCER IMMUNOLOGY/IMMUNOTHERAPY

Assistant Professor/Associate Professor/Professor

Mayo Clinic Cancer Center
Phoenix/Scottsdale, Arizona

The Mayo Clinic Cancer Center, an NCI-designated Comprehensive Cancer Center, seeks an outstanding investigator in the area of cancer immunology and/or immunotherapy. This position will be based at Mayo Clinic's research facilities in Phoenix/Scottsdale, AZ, which currently have 15 independent research laboratories with expertise in immunology, molecular biology, genomics, oncogenic signaling mechanisms, molecular mechanisms of carcinogenesis and molecular mechanisms of tumor cell invasion and metastasis. The Center seeks candidates whose research focuses on advancing basic aspects of cancer immunology/immunotherapy and translating these advances into novel treatments of cancer. Investigators focusing on clinical-immunology with experience for the evaluation of the human immune system are encouraged to apply. The ability of the candidate to work as a part of an integrated, multidisciplinary team is essential. It is anticipated that the successful candidate will also participate in the institution-wide Cancer Immunology program with colleagues from Mayo Clinic's Rochester and Jacksonville campuses. Applicants at either a senior or junior level are encouraged to apply. The position offers an outstanding start-up package, research space and annual operating funds, and a very competitive personal compensation and benefits package.

To learn more about the Mayo Clinic Cancer Center, visit our website: **http://mayoresearch.mayo.edu/mayo/research/cancercenter/**. For general information about Mayo Clinic, including its Arizona campus, please visit the website: **www.mayoclinic.org**.

Applicants should send their curriculum vitae, a description of research focus and the name of three references to:

Joseph Lustgarten, Ph.D.
Associate Professor, Department of Immunology, Mayo Clinic College of Medicine:
lustgarten.joseph@mayo.edu

Mayo Clinic is an affirmative action and equal opportunity educator and employer. Post offer/pre-employment drug screening is required.

Center for Immunology and Microbial Disease Albany Medical College

Faculty Position

The Center for Immunology and Microbial Disease at Albany Medical College invites applications for a tenure-track faculty position from individuals who have a doctoral degree, postdoctoral experience, and demonstrated research productivity. Those with an interest in bacterial pathogenesis and host-pathogen interactions are particularly encouraged to apply. The successful candidate will be expected to establish an independent, extramurally funded research program and participate in the teaching of medical and graduate students. The basic science departments at Albany Medical College are organized as interdisciplinary research centers and the Center for Immunology and Microbial Disease has a focus on microbial pathogenesis and immune defense, particularly as related to biothreat agents and emerging infections. Faculty at the Albany Medical College receive competitive salaries, attractive start-up packages, and access to the Center's ABSL-3/BSL-3, Microbiology and Immunology Core Labs. In addition, we have established a close relationship with the New York State Department of Health Wadsworth Laboratories, providing a diverse environment that is rich in infectious disease expertise. Albany Medical College is located in a mid-sized city within the upstate New York Capital Region, and has easy access to Boston, New York City, and the Adirondack Mountains.

Applicants should send their curriculum vitae, a statement of research plans, and three letters of reference to: **Dennis W. Metzger, Ph.D., Professor, Theobald Smith Alumni Chair and Director, Center for Immunology and Microbial Disease, Albany Medical College, 47 New Scotland Avenue, MC-151, Albany, NY 12208.** For further information about the Center, visit **www.amc.edu/Academic/Research/imd.htm**.

An Equal Opportunity/Affirmative Action Employer.
Women and minorities are encouraged to apply.

UNIVERSITY OF MICHIGAN

SCHOLARS PROGRAMS

BIOLOGICAL SCIENCES SCHOLARS PROGRAM
For Junior, Tenure-Track Faculty

The University of Michigan announces recruitment for the Biological Sciences Scholars Program (BSSP) to continue to enhance its investigational strengths in the life sciences research programs.

Now entering its 11th year, this Program has led to the recruitment of outstanding young scientists in the areas of genetics, microbiology, immunology, virology, structural biology, pharmacology, biocheistry, molecular pharmacology, stem cell biology, physiology, cell and developmental biology, and the neuosciences. The Program seeks individuals with PhD, MD, or MD/PhD degrees, at least two years of postdoccoral research experience, and evidence of superlative scientific accomplishment and scholarly promise. Successful candidates will be expected to establish a vigorous, externally-funded research program, and to become leaders in departmental and program activities, including teaching at the medical, graduate, and/or undergraduate levels. Primary college and department affiliation will be determined by the applicant's qualifications and by relevance of the applicant's research program to departmental initiatives and focus. All faculty recruited via the BSSP will be appointed at the Assistant Professor level.

APPLICATION INSTRUCTIONS: Please apply to the Scholars Programs through the BSSP web site at: (http://www.med.umich.edu/medschool/orgs/bssp). A curriculum vitae (including bibliography), a three-page research plan, an NIH biosketch, and three original letters of support should all be submitted through the BSSP web site. More information about the Scholars Programs, instructions for applicants and those submitting letters of recommendation, and how to contact us is located on the BSSP web site: (http://www.med.umich.edu/medschool/orgs/bssp). The final deadline for applications is Friday, October 19, 2007, 5:00 pm EDT.

The University of Michigan is an Affirmative Action/Equal Opportunity Employer.

Faculty Position
Cell Biology Program
Sloan-Kettering Institute

The Cell Biology Program, Sloan-Kettering Institute (www.ski.edu) has initiated a search for tenure-track faculty members. We are interested in outstanding individuals who have the potential to develop an innovative, independent research program that complements and enhances our existing strengths. Candidates with research interests in exciting areas of eukaryotic cell biology and using a variety of experimental approaches and systems are encouraged to apply. New faculty will be eligible to hold graduate school appointments in the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences, the Weill Graduate School of Medical Sciences of Cornell University, as well as the Tri-Institutional MD/PhD Training Program. Sloan-Kettering has an outstanding infrastructure as well as state-of-the-art core resources, and we are now significantly expanding our research programs.

Interested individuals should e-mail their application, preferably in PDF format, to: **cellbio@mskcc.org** by November 15, 2007. The application should include a Curriculum Vitae, a description of past research, a description of proposed research, and copies of three representative publications. Candidates should arrange to have three signed letters of recommendation sent by e-mail to: **cellbio@mskcc.org** and by postal mail to: **Cell Biology Search, c/o Tiffany Lennon, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 135, New York, NY 10065.** The letters should arrive by November 15, 2007. Inquiries can also be made by e-mail to: **cellbio@mskcc.org.** EOE/AA.

Memorial Sloan-Kettering Cancer Center
The Best Cancer Care. Anywhere.
www.mskcc.org

DUKE NUS
GRADUATE MEDICAL SCHOOL SINGAPORE

Faculty Positions
Cancer and Stem Cell Biology

The Duke-NUS Graduate Medical School Singapore (Duke-NUS GMS), a global partnership between the Duke University and the National University of Singapore, is recruiting internationally. We seek creative scientists who are focusing on discovery biology and/or translational medicine in the field of **Cancer and Stem Cell Biology.**

Applicants for all ranks should have a PhD, MD, or equivalent and a record demonstrating outstanding promise. Special opportunities exist for research involving cancer stem cells, advanced imaging, and translational studies both in non-human primates and in collaboration with world-class clinical services, including Singapore's National Cancer Centre and General Hospital. Successful applicants will join investigators already affiliated with Duke-NUS GMS (see www.gms.edu.sg). Faculty positions include full salary, generous start-up, and research funding of up to S$500K/p.a., assuring a stable base of support that can be supplemented by competitive grant awards, which are expanding rapidly in Singapore.

Interested candidates should send a cover letter, curriculum vitae, a summary of research accomplishments and future plans, and arrange for three letters of reference to be forwarded (Assistant Professor candidates), no later than 9 November 2007, to:

David Virshup, Director
Program in Cancer and Stem Cell Biology
Duke-NUS Graduate Medical School Singapore
2 Jalan Bukit Merah, Singapore 169547
email to: CSB.recruit@gms.edu.sg

Igniting the Pioneer Spirit

BOWDOIN COLLEGE

Director of the Bowdoin Scientific Station on Kent Island

Bowdoin College invites applications for a position as Director of the Bowdoin Scientific Station on Kent Island, New Brunswick, beginning **Spring 2008**. This non-tenurable, 12-month position is renewable at five-year intervals.

Ph.D. required, postdoctoral experience preferred. The Director is expected to pursue an active summer research program on Kent Island on any aspect of terrestrial or marine science, involve and mentor undergraduates in field research, and serve as a resource for visiting scientists. Responsibilities include seeking external funding to support the field station, recruiting faculty, graduate and undergraduate student researchers, communicating with alumni, and spending at least one semester on campus per year while offering one course in his or her field of interest.

Please submit letter of application, curriculum vitae, and a description of your research interests and teaching philosophy. Bowdoin College is accepting electronic submissions or paper submissions; however, electronic submissions are strongly encouraged. To submit electronically, please visit **Careers@Bowdoin.edu (https://careers.bowdoin.edu/applicants/Central?quickFind=50569)**

Three letters of reference should be sent via e-mail to: **acadaffs@bowdoin.edu** or by mail to: **Chair, Bowdoin Scientific Station Director Search Committee**
5800 College Station
Bowdoin College
Brunswick, ME 04011-8465

Paper submissions can be sent to this address as well. Review of applications will begin **November 1, 2007.**

Bowdoin is a highly selective liberal arts college on the Maine coast with a diverse student body made up of 25% students of color, 4% International students and approximately 15% first generation college students. For further information about the college and the field station, see our website at

Bowdoin

www.bowdoin.edu

DEVELOPMENTAL BIOLOGY

The Department of Biology at American University invites applications for a **TENURE TRACK** position at the Assistant Professor level to begin Fall, 2008. A Ph.D. in Developmental Biology or closely related field, an established record or outstanding potential for research, and teaching experience are required. Responsibilities include teaching biology courses for majors and non-majors and advanced courses in developmental biology, developing a strong research program, supervising undergraduate and graduate student research, and providing university service.

Submit a letter of application, curriculum vitae, brief summary of research plan, and statement of teaching philosophy and have three letters of reference sent directly from the referees to: **Dr. Daniel Fong, Developmental Biology Search Committee Chair, Department of Biology, American University, 4400 Massachusetts Avenue, N.W., Washington, D.C. 20016-8007, USA**; electronic submission to **biology@american.edu** with **"Developmental Biology Search"** on subject line. Review of applications will begin on **November 1, 2007**, and continue until the position is filled. American University is seeking highly dedicated teachers and scholars who are deeply committed to interdisciplinary learning, the application of new technologies in teaching and scholarship, and to the preparation of students for life in a diverse and rapidly changing global society.

American University is an Affirmative Action Equal Opportunity Employer, committed to a diverse faculty, staff and student body. Women and minority candidates are strongly encouraged to apply.

The University of Texas at Austin

ASSISTANT PROFESSOR in Prokaryotic Molecular Genetics

The Section of Molecular Genetics and Microbiology at the University of Texas at Austin invites applicants for a tenure-track faculty position in prokaryotic molecular genetics at the Assistant Professor level. Outstanding applicants at the rank of Associate or Full Professor will also be considered. The Section has a scientifically diverse faculty and all areas will be considered. All areas will be considered but applicants studying gram-positive or pathogenic bacteria or with interests in systems biology approaches are especially encouraged to apply. We seek an outstanding investigator who will build an active research program and will teach effectively at the undergraduate and graduate levels. The successful candidate will be eligible for membership in the Institute for Cellular and Molecular Biology, will have access to its extensive core facilities, and will have the opportunity to participate in several graduate programs. The position offers excellent start-up funds, salary and laboratory space in a new building that is part of a dynamic, highly interactive research environment.

Please send a single PDF file containing your curriculum vitae, summary of research interests, and names of three references before January 1, 2008 to: mgm_search@biosci.utexas.edu. References may also send their letters directly to the same email address.

Homepages • http://www.biosci.utexas.edu/mgm/
http://www.icmb.utexas.edu

The University of Texas at Austin is an Equal Opportunity Employer
Qualified women and minorities are encouraged to apply
a background check will be conducted on the applicant selected.

University of Louisville James Graham Brown Cancer Center's Owensboro Cancer Research Program (OCRP) Faculty Position

The University of Louisville James Graham Brown Cancer Center and the Owensboro Cancer Research Program (OCRP) invite applications for a tenure-track faculty position in translational cancer research at the **ASSISTANT** or **ASSOCIATE PROFESSOR** level. The successful candidate will join the OCRP and be located in newly constructed laboratory space at the Mitchell Memorial Cancer Center, Owensboro, Kentucky. The OCRP represents a new translational research program focused on combining the field of plant-made pharmaceuticals with the prevention and treatment of cancer. Applicants must have a M.D., Ph.D., or Ph.D. with postdoctoral research experience, a strong track record of publications, and will be expected to establish an independently funded research program. Associate Professor candidates must demonstrate a history of successful funding. Candidates with research interests in the areas of molecular target discovery, cancer vaccines, therapeutic antibodies and cell-based cancer therapies are particularly encouraged to apply.

Please send curriculum vitae, with a bibliography, a synopsis of research interests, and the names and telephone/facsimile/e-mail of at least three references to:

Keith R. Davis, Chair
Faculty Search Committee
Owensboro Cancer Research Program
Mitchell Memorial Cancer Center, Suite 201
1020 Breckenridge Street
Owensboro, KY, 42303

or by Email: **facultysearch@ocrp.org**

Review of applications will begin immediately and continue until the position is filled.

The University of Louisville is an Affirmative Action, Equal Opportunity Employer.

The University of Texas at Austin

Eukaryotic Molecular Biology Positions

The Institute for Cellular and Molecular Biology

The Institute for Cellular and Molecular Biology, Alan Lambowitz, Director, invites applications for two tenure-track/tenured positions in eukaryotic molecular biology. Academic appointments at the level of Assistant, Associate, or Full Professor will be in an appropriate academic unit in the College of Natural Sciences. Candidates should have an outstanding record of research productivity and a research plan that utilizes molecular and biochemical approaches to address important problems in eukaryotic molecular biology. Areas of particular interest include but are not limited to chromatin structure, regulation of gene expression, microRNAs and RNA interference, DNA damage responses, and cell cycle control.

Building on a strong existing faculty, the Institute has recruited more than 45 new faculty members over the past nine years (see www.icmb.utexas.edu). In addition to it's highly interactive and interdisciplinary research environment, the Institute provides administrative and financial support for the Graduate Program in Cell and Molecular Biology and state-of-the-art core facilities including DNA sequencing, mass spectrometry, electron and confocal microscopy, DNA microarrays, robotics, and mouse genetic engineering. A recently instituted MD-PhD program with the UT Medical Branch and the new Dell Pediatrics Research Institute further enhance the environment for basic Biomedical Research.

Austin is located in the Texas hill country and is widely recognized as one of America's most beautiful and livable cities.

Please apply on-line at http://www.icmb.utexas.edu/apply/between Sept. 1 and Nov. 1, 2007.

The University of Texas at Austin is an Equal Opportunity Employer. Qualified women and minorities are encouraged to apply; a background check will be conducted on applicant selected.

Tufts University

TENURE TRACK FACULTY POSITION
MOLECULAR EVOLUTION

The Department of Biology at Tufts University invites applications for a tenure-track Assistant Professor in Molecular Evolution beginning in September, 2008. Research areas might include evolutionary genetics, molecular phylogenetics, evolutionary development, or gene regulatory networks. Preference will be given to candidates with strong bioinformatics training and approaches, whose research will complement current departmental strengths in genome stability, developmental biology, behavior, physiology, or population ecology (see **http://ase.tufts.edu/biology/**). The successful candidate is expected to develop an active externally funded research program involving graduate and undergraduate students. Teaching responsibilities will include contributing to undergraduate and graduate level courses in evolution and other departmental courses. Doctoral degree and a record of research productivity required.

Applicants should submit curriculum vitae, three recent publications, separate statements of (1) research interests and plans and (2) teaching experience and plans, and have three letters of reference sent to: **Chair, Molecular Evolution Search Committee, Department of Biology, Tufts University, Medford, MA 02155**. Review of applications begins **November 15, 2007** and continues until the position is filled.

Tufts University is an Affirmative Action/Equal Opportunity Employer. We are committed to increasing the diversity of our faculty. Members of underrepresented groups are strongly encouraged to apply.

Yale University School of Medicine
Interdepartmental CNNR Program
Cellular Neuroscience, Neurodegeneration, and Repair
PO Box 9812
New Haven, CT 06536-0812
http://info.med.yale.edu/cnnr

Faculty Positions
Neurodegeneration and Neural Repair

The newly established Yale Program for Cellular Neuroscience, Neurodegeneration, and Repair (CNNR) is searching for scientists involved in basic and translational disease research focused on **Neurodegeneration and Neural Repair**. Successful applicants will receive a primary appointment in one of the departments of the Yale School of Medicine and will be active members of their department.

The overall goals of the Program are to:
(a) understand neuron-specific aspects of cell function,
(b) elucidate the cellular pathophysiology of neurodegeneration and
(c) translate this knowledge into therapies capable of repairing the nervous system and improving neuronal function in disease.

The Program emphasizes molecular and genetic approaches and fosters interactions across disciplinary boundaries. See our website **http://info.med.yale.edu/cnnr**.

Candidates must hold an M.D. and/or a Ph.D. degree, or equivalent degrees. We invite applications at the rank of assistant professor, but appointments at the rank of associate and full professor will be considered. This round of applications is due by **November 15, 2007**. Please send a cover letter, curriculum vitae, up to 3 representative publications, a research plan (strictly limited to 2 pages), and arrange for submission of 3 letters of recommendation. Application materials should be sent **electronically** to **Pietro De Camilli** and **Stephen M. Strittmatter**, directors of the Program, exclusively at the following e-mail address: **cnnr.search@yale.edu**. Recommendation letters can be forwarded by mail.

Applications from, or nominations of, women and minority scientists are encouraged. Yale is an Affirmative Action/Equal Opportunity Employer.

Yale University School of Medicine
Interdepartmental CNNR Program
Cellular Neuroscience, Neurodegeneration, and Repair
PO Box 9812
New Haven, CT 06536-0812
http://info.med.yale.edu/cnnr

Faculty Positions
Basic Neuroscience

The newly established Yale Program for Cellular Neuroscience, Neurodegeneration, and Repair (CNNR) is searching for scientists involved in **Basic Neuroscience** research. Successful applicants will receive a primary appointment in one of the basic science departments of the Yale School of Medicine and will be active members of their department.

The Program emphasizes molecular, genetic and biophysical approaches to expand knowledge of neuron-specific aspects of cell function and fosters interactions across disciplinary boundaries. See our website **http://info.med.yale.edu/cnnr**.

Candidates must hold an M.D. and/or a Ph.D. degree, or equivalent degrees. We invite applications at the rank of assistant professor, but appointments at the rank of associate and full professor will be considered. This round of applications is due by **November 15, 2007**. Please send a cover letter, curriculum vitae, up to 3 representative publications, a research plan (strictly limited to 2 pages), and arrange for submission of 3 letters of recommendation.

Application materials should be sent **electronically** to **Pietro De Camilli** and **Stephen M. Strittmatter**, directors of the Program, exclusively at the following e-mail address: **cnnr.search@yale.edu**. Recommendation letters can be forwarded by mail.

Applications from, or nominations of, women and minority scientists are encouraged. Yale is an Affirmative Action/Equal Opportunity Employer.

E.I DuPont de Nemours and Company, Inc. is expanding its technology and engineering capabilities and is locating a Research and Development facility within its wholly-owned subsidiary, E.I. DuPont, India, in the Hyderabad area. As part of this plan, we are establishing an Industrial Biotechnology Research and Development group in the Hyderabad which will focus on a broad range of activities associated with the production of fuels, chemicals, and materials from renewable resources using modern tools of molecular biology, biochemistry, and fermentation sciences. We are currently seeking candidates to lead this group.

DuPont science helps Industrial Biotechnology come of age in India with YOU at the helm

Project Lead for Industrial Biotechnology:

The successful candidate will have a demonstrated record of research accomplishments in molecular biology, biochemistry, or fermentation science, and demonstrated program and administrative leadership experience. The Project Lead will be expected to recruit a highly skilled R&D workforce and work closely with our on-site team in finalizing the construction and outfitting of our state-of-the-art research facilities. She or he also will work collaboratively with research leadership in our labs in the US to develop research plans which will deliver results for a portfolio of ongoing programs, including those that apply to the Indian sub-continent, and articulate and develop new technical approaches. In addition, the Project Lead will interact with leaders of the plant biotechnology research teams located in Hyderabad to maximize productivity while creating a world-class research capability. Responsibilities also include interacting with other companies and institutions in India to assess opportunities for collaborations in areas of interest that may arise.

Qualifications:

• Ph.D. in chemistry, biology, microbiology, chemical or biological engineering • Strong focus and interest in developing new chemicals and materials from renewable resources • Demonstrated research productivity in at least one of microbial molecular biology, enzymology, microbiology, or fermentation science • Minimum of five years experience leading multidisciplinary, project-oriented research teams, including supervising other research scientists • Excellent written and oral communication skills.

The above position is **Permanent** in nature. The remuneration will be based upon experience and qualification and is commensurate with the best in the industry.

DUPONT *The miracles of science™*

Qualified candidates should apply through DuPont's career web-page: http://careers.dupont.com Click on: jobs by region/Asia Pacific/India. Enter the code RES00512 in the keyword field.

UNIVERSITY OF PENNSYLVANIA

Faculty Positions, Abramson Family Cancer Research Institute

The Abramson Family Cancer Research Institute at the University of Pennsylvania's School of Medicine seeks candidates for an Associate or Full Professor position in the tenure track. Rank will be commensurate with experience. Applicants must have an M.D. and/or Ph.D degree and have demonstrated excellent qualifications in Education and Research.

The Abramson Family Cancer Research Institute is an integral part of the Abramson Cancer Center of the University of Pennsylvania. Faculty appointment will be made in an appropriate department of the School of Medicine.

Candidates may have scientific interest and experience in any field of cancer biology, including but not limited to cancer genetics and genomics, cancer cell metabolism, tumor microenvironment, and cancer cell biology.

Responsibilities will include the development of an independent research program. Qualifications and experience in teaching are required.

The University of Pennsylvania is an equal opportunity, affirmative action employer. Women and minority candidates are strongly encouraged to apply.

Please submit curriculum vitae, a cover letter, 3 reference letters, and a statement of research interests to:

M. Celeste Simon, Ph.D.
Scientific Director
The Abramson Family
Cancer Research Institute
456 BRB II/III, 421 Curie Boulevard
Philadelphia, PA 19104
afcrirec@mail.med.upenn.edu
www.uphs.upenn.edu/abramson

Leonard & Madlyn ABRAMSON *family* CANCER RESEARCH INSTITUTE at the University of Pennsylvania Cancer Center

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UNIVERSITY OF PENNSYLVANIA Abramson Cancer Center

FACULTY POSITIONS

School of Medicine, Department of Cancer Biology

The Department of Cancer Biology at the University of Pennsylvania's School of Medicine seeks candidates for an Assistant, Associate, and/or Full Professor position in the tenure track. Rank will be commensurate with experience. Applicants must have an M.D. and/or Ph.D degree and have demonstrated excellent qualifications in Education and Research.

The Department of Cancer Biology is an integral part of the University of Pennsylvania Abramson Cancer Center and the School of Medicine. Qualified applicants may have scientific interests and experience in any field of cancer biology, including but not limited to cancer stem cells, cancer genetics and genomics, tumor microenvironment, angiogenesis, cancer cell metabolism, cancer cell biology, and oncogenic signaling.

Responsibilities will include the development of an independent research program. Qualifications and experience in teaching are required.

The University of Pennsylvania is an equal opportunity, affirmative action employer. Women and minority candidates are strongly encouraged to apply.

Please submit curriculum vitae, a cover letter, 3 reference letters, and a statement of research interests to:

Lewis A. Chodosh, M.D., Ph.D.
Professor and Interim Chair, Department of Cancer Biology
6th Floor - BRB II/III, 421 Curie Boulevard, Philadelphia, PA 19104
cbiorecr@mail.med.upenn.edu

Peking University, in collaboration with the Temasek Life Sciences Laboratory (Singapore), seeks to hire **Principal Investigators** to lead research groups in the field of developmental biology. Preference will be given to candidates using animal model systems (including, but not limited, to *C. elegans*, *Drosophila melanogaster*, and zebrafish). Successful applicants will be provided with a generous start-up package and an interactive environment to foster research.

Applicants are expected to have a proven track record of research accomplishments and potential for carrying out independent cutting edge research. To apply, send a complete CV, a research plan (not to exceed 3 pages), and arrange for three letters of recommendation mailed directly from referees to **Ms. Wei Dong, Center of Genetics and Developmental Biology, College of the Life Sciences, Peking University, Beijing 100871, P.R. China**. E-mail: **dongwei@pku.edu.cn.** More information about the PKU-TLL Joint Lab can be found on our websites: **http://www.bio.pku.edu.cn/employ/develop** or **http://genetics-development.spaces.live.com**. For best consideration, applications must be received by **December 31, 2007**; however, position will remain open until filled.

PKU and TLL is an Equal Opportunity/Affirmative Action employer and provide excellent pay and benefits.

University of Michigan
Center for
stem cell biology

The Life Sciences Institute and the University of Michigan Medical School invite applications for tenure track **ASSISTANT PROFESSOR** positions. We are seeking outstanding scholars, with Ph.D., M.D. or equivalent degrees and relevant postdoctoral experience, who show exceptional potential to develop an independent research program that will address fundamental issues in any aspect of stem cell biology. Applicants who have already established successful independent research programs will be considered for tenured **ASSOCIATE PROFESSOR** or **PROFESSOR** positions.

Applicants should send a curriculum vitae, copies of up to three reprints, a one- to two-page summary of research plans, and arrange to have three letters of reference sent directly by **November 1, 2007** to:

Stem Cell Search Committee
c/o Rebecca Fritts
Life Sciences Institute
University of Michigan
210 Washtenaw Avenue
Ann Arbor, Michigan, 48109-2216

The University of Michigan is an Affirmative Action/ Equal Opportunity Employer.

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

Neuroscience Faculty Recruitment

The Department of Neuroscience at Columbia University Medical Center, as part of a University-wide Neuroscience Initiative, is recruiting faculty concentrating on the analysis of neural circuitry through molecular, genetic, cellular electrophysiological, and/or imaging approaches. We are particularly interested in individuals whose research program explores neural circuits in genetically tractable model systems and in the context of well-defined behaviors. We encourage applications for positions at the Assistant Professor level but will also consider applications from more senior investigators for positions at the level of Associate or Full Professor.

Columbia University currently has a world-renowned program in neurobiology and behavior, and the Neuroscience Initiative aims to enhance interactions between basic and clinical neurosciences and link the neurosciences to other scientific disciplines within the University. Faculty will be affiliated with the Department of Neuroscience, and there will be opportunities for strong ties with scientific departments and programs on the Morningside Heights campus.

Applications for this round of recruitment are requested by November 1, 2007. A CV, cover letter including statement of interests, and three letters of reference sent separately should be e-mailed care of David Leyden, dgl2102@columbia.edu. In addition, please mail a hard copy of these documents to:

Chair, Neuroscience Search Committee
c/o: David Leyden
Columbia University
Hammer Health Sciences Center
Room 2-205G
701 West 168th Street
New York, NY 10032

Columbia University takes affirmative action to ensure equal employment opportunity.

FACULTY POSITIONS
BAYLOR COLLEGE OF MEDICINE

The Department of Molecular Physiology and Biophysics at Baylor College of Medicine is seeking scientists with outstanding records of research accomplishment for faculty positions at the Assistant (tenure-track), Associate or Full Professor level. Ideal candidates will develop a strong independent research program and be committed to excellence in graduate and medical student education. Candidates employing advanced technologies for studying metabolism, diabetes, the cardiovascular system or cancer biology in vertebrate models of human disease are particularly encouraged to apply. The department has a strong commitment to both basic and translational biomedical research and has state-of-the-art facilities for confocal and multiphoton imaging, mouse MRI, computed tomography and cores for the creation and phenotypic analysis of new mouse models. Baylor College of Medicine is a world-renowned research institution with strengths in many areas and ample opportunities exist for scientific interaction and collaborations within the department, throughout the College, and with the other world class institutions of the Texas Medical Center.

Applications will be reviewed beginning **November 15, 2007** until the positions are filled. Please email your application materials to **molphys@bcm.edu** and include a curriculum vitae and a description of your current and future research program. Candidates for a junior position should have three letters of references sent separately to the same email address or to:

Dr. Henri Bayle
Department of Molecular Physiology and Biophysics
Baylor College of Medicine
One Baylor Plaza, BCM335
Houston, TX 77030

Baylor College of Medicine is an Equal Opportunity, Affirmative Action, and Equal Access Employer.

Assistant/Associate Professor of Bioinformatics/ Computational Biology

Department of Biostatistics

Harvard School of Public Health

The Department of Biostatistics at Harvard School of Public Health (HSPH), is seeking an outstanding candidate for a tenure-track faculty position in Bioinformatics/Computational Biology at the level of Assistant or Associate Professor. The successful candidate would join an active group at HSPH developing novel computational and statistical methods, and conduct collaborative research with clinical and basic scientists at Harvard University and its affiliated medical centers. She/he is expected to play a vital leadership role in expanding the quantitative science research and educational programs at HSPH in bioinformatics and computational biology and its related fields. Candidates should have doctoral degree and a demonstrated record of achievement; candidates in all areas of computational biology, bioinformatics and statistical science are encouraged to apply. Please send a letter of application, including a statement of current and future research interests, a curriculum vitae, sample publications, and the names of three referees to the address below. Applicants should ask their three referees to write independently to this address.

Computational Biology Junior Faculty Search Committee
Department of Biostatistics
Harvard School of Public Health
655 Huntington Avenue, 4th Floor
Boston, MA 02115

Harvard School of Public Health is strongly committed to increasing the representation of women and minority members among its faculty and particularly encourages applications from such candidates.

Center for Metabolism and Obesity Research Johns Hopkins University

The **Institute for Basic Biomedical Sciences** at **The JHU School of Medicine** has initiated a major initiative to recruit new faculty and create cross-disciplinary and highly interactive research centers.

The mission of the Center for Metabolism and Obesity Research (CMOR) is to study and support integrative research in the field of metabolism and systems biology. Our objective is to advance our understanding of the biological mechanisms that regulate metabolism and how they are dysregulated in attendant disorders, such as obesity and diabetes. CMOR seeks to recruit faculty interested in applying in vitro and in vivo models to further our understanding of the regulation of energy sensing, nutrient sensing, and endocrine responses and how these processes are altered by disease. Our goal is to create a multidisciplinary and collegial center.

Applicants should submit an application by January 15, 2008 via email (IBBScenters@jhmi.edu). Include a CV, research plan, names of three references and up to three publications (all in pdf format). Indicate **CMOR** in the subject line.

The Johns Hopkins University is committed to diversity and equality in education and employment and encourages applications from under-represented groups.

D. E. Shaw Research, LLC

Early Career Scientists and Engineers: Computational Biochemistry Research Group

Extraordinarily gifted early career scientists and engineers sought to join a rapidly growing New York–based research group pursuing an ambitious, long-term project aimed at achieving major scientific advances in the field of biochemistry and fundamentally transforming the process of drug discovery. Successful candidates will work closely with a number of the world's leading biologists, chemists, and computer scientists, and will have the opportunity not only to participate in an exciting entrepreneurial venture with considerable economic potential, but to make groundbreaking contributions within the fields of biology, chemistry, and medicine.

D. E. Shaw Research, LLC, is seeking scientists and engineers with zero to five years of experience who have degrees in chemistry, biology, physics, computer science, engineering, and mathematics from top-tier universities. Serious consideration will be given to candidates with extraordinary records of achievement in the natural sciences and/or scientific programming, exceptional quantitative abilities, and superb communication skills.

The group's current research activities are aimed at the discovery and development of innovative scientific techniques to direct unprecedented computational power toward the solution of key problems in the fields of biomolecular simulation and design. This research effort is being financed by the D. E. Shaw group, a global investment and technology development firm with more than US $30 billion in aggregate investment capital. The project was initiated by the firm's founder, Dr. David E. Shaw, and operates under his direct scientific leadership.

We are prepared to offer above-market compensation to candidates of truly exceptional ability. Interested applicants should send a resume to:

sciencemag-sa@career.deshawresearch.com.

D. E. Shaw Research, LLC does not discriminate in employment matters on the basis of race, color, religion, gender, pregnancy, national origin, age, military service eligibility, veteran status, sexual orientation, marital status, disability, or any other protected class.

DE Shaw & Co

Brown University
Center for Computational Molecular Biology
Faculty Position

Brown University seeks highly qualified candidates for one open rank, tenure-track or tenured faculty position with a preference for assistant professor in the Center for Computational Molecular Biology (CCMB). The growing CCMB currently has four full-time faculty members, two in Computer Science, one in Applied Mathematics and one in Biology. Candidates are sought in all areas of computational biology and bioinformatics, particularly those who specialize in research areas complementary to and synergistic with those of current faculty. The research areas of the current Center faculty are: algorithmic methods and statistical inference in genomics, comparative genomics and evolution, gene regulatory networks, regulatory genomics, mathematical models of genetic variation, and cancer genomics.

The successful applicant will be expected to have a demonstrated potential for excellence in research and have outstanding teaching skills. Junior faculty applicants should show the potential to establish an externally funded research program; senior faculty applicants should have established such a program. The appointee will participate in the continuing development of Brown's established undergraduate Computational Biology curriculum and a newer graduate curriculum built upon the foundation of Brown's widely recognized record of teaching innovation and academic excellence. The appointee will have the opportunity to participate in several interdisciplinary projects, including collaborations with faculty in the Center for Genomics and Proteomics, the Center for Cardiovascular Research and other multidisciplinary programs at Brown and affiliated hospitals. The appointment will be in one of the following top-ranked departments: Division of Applied Mathematics, Department of Computer Science, or Division of Biology and Medicine.

Applicants should submit curriculum vitae, representative preprints or reprints, and their research and teaching plans with emphasis on their interdisciplinary expertise. Additionally, candidates for Assistant Professor should arrange to have at least three letters of recommendation sent directly to the contact address. Candidates for Associate or Full Professor should provide names and contact information for at least five references, who will be contacted for letters of recommendation by the search committee at an appropriate time. All applications will be treated confidentially. Application review will commence on **December 10, 2007** and continue until the position is filled.

All documents should be sent electronically in PDF to: **ccmbfs@cs.brown.edu**. In addition, please send the cover letter and letters of recommendation to: **Sorin Istrail ~ Chair, CCMB Search Committee, Center for Computational Molecular Biology, Brown University, Box 1910, 115 Waterman Street, Providence, RI 02912.**

For further information, see http://www.brown.edu/Research/CCMB

Brown University is an Affirmative Action/Equal Opportunity Employer. Women and minorities are encouraged to apply.

Faculty Position
Neuroscience Research
Department of Pediatrics
University of Maryland
School of Medicine

A tenure track position is available to highly qualified individuals with interests that complement and extend research in the department. The successful candidate will interact with ongoing research on developmental brain metabolism including preclinical studies on neuroprotection in hypoxia/ischemia, excitotoxic damage, and traumatic brain injury, and will mentor young faculty and fellows in research. Resources include a Brain and Tissue Bank for Developmental Disorders, and NMR spectroscopy for studies of brain function and metabolism. The University has outstanding research in neuroscience and neuroprotection and offers competitive salary, benefits and start up funds. Qualified candidates with a Ph.D and/or M.D. degree and external funding should apply by **December 1, 2007**. Applicants should send a CV, a 3-page summary of research accomplishments and future plans, and the email addresses of three references to **Dr. Mary McKenna** at **mmckenna@umaryland.edu**. Position **#03314327**.

The University of Maryland is an Equal Opportunity, Affirmative Action Employer.

PREDOCTORAL AND POSTDOCTORAL FELLOWSHIPS IN TRANSLATIONAL CARDIOVASCULAR RESEARCH

Predoctoral and postdoctoral positions are available at Columbia University College of Physicians and Surgeons in the Department of Physiology and Cellular Biophysics and the Wu Center for Molecular Cardiology, with support available from a NHLBI T32 Institutional NRSA award. Twenty-eight basic and clinical Cardiovascular laboratories are part of this training program that focuses on the following areas: (1) Cardiovascular Cell Biology; (2) Cardiovascular Biophysics; (3) Genetics and Genomics; (4) Bio- and Tissue-Engineering; (5) Computational Biology; (6) Translational Cardiovascular Research. The training program has well-established cardiovascular seminars, journal clubs, joint laboratory meetings and retreats, designed to encourage collaborations and foster excellence in cardiovascular research.

For more information please visit our website:
http://cpmcnet.columbia.edu/dept/physio/training.html

For predoctoral positions, applications can be completed on-line at:
http://cpmcnet.columbia.edu/dept/physio/graduate_program.html

Questions related to the Physiology graduate program can be emailed to:
graduateprogram@columbiaphysiology.org

For postdoctoral positions, applicants must have a Ph.D. and/or M.D. Please email your letter of interest, curriculum vitae and three recommendations letters to:

Andrew R. Marks, M.D.
Chair, Physiology and Cellular Biophysics
Principal Investigator, Multidisciplinary Training Program in Translational Cardiovascular Research
cardiovascular@columbiaphysiology.org

All applicants must be U.S. citizens or permanent residents. Minority and female applicants are particularly encouraged to apply.

Penn
University of Pennsylvania

Institute for Diabetes, Obesity and Metabolism and the Department of Cell and Developmental Biology, Assistant/Associate Professor Tenure Track

The Institute for Diabetes, Obesity and Metabolism (IDOM) and the Department of Cell and Developmental Biology at the University of Pennsylvania's School of Medicine seek candidates for Assistant or Associate Professor position in the tenure track. Rank will be commensurate with experience. Applicants must have an M.D, Ph.D. or M.D./Ph.D. and have demonstrated excellent qualifications in Education and Research. Qualifications and experience in teaching will be required. Developing an independently funded research program will be required for promotion in the tenure track.

The successful applicant will receive an excellent start-up package and move into newly renovated space in a superb scientific environment.

Qualified applicants must have demonstrated research productivity related to diabetes or obesity. We are particularly interested in individuals who will complement existing strengths of the Penn IDOM, using novel cell-based systems and/or model organisms. For more information visit the IDOM website at **http://www.med.upenn.edu/idom/** and the Cell and Developmental Biology website at **http://www.med.upenn.edu/cellbio/**.

Please send curriculum vitae, letter of research interest and three letters of reference to:

Mitchell A. Lazar, M.D., Ph.D.
Professor of Medicine and Chief of Endocrinology, Diabetes and Metabolism
Director, Institute for Diabetes, Obesity and Metabolism
c/o Ms. Kishani Martin
University of Pennsylvania School of Medicine
700 Clinical Research Building
415 Curie Boulevard
Philadelphia, PA 19104-6149

The University of Pennsylvania is an Equal Opportunity, Affirmative Action Employer. Women and minority candidates are strongly encouraged to apply.

ECOLOGY

University of California San Diego
Section of Ecology, Behavior and Evolution
Division of Biological Sciences
http://www-biology.ucsd.edu/

The EBE section and the Division of Biological Sciences are committed to building a strong program in environmental biology to meet the key challenges of the 21st century. We seek applications from scientists working to understand and solve ecological problems both locally and globally that are caused by human impacts. Applications from junior candidates are strongly encouraged although tenured scientists will be considered. Area of scholarship is open, but we are particularly interested in candidates working in the areas of global change biology and human impacts on community structure and dynamics. Applicants should demonstrate outstanding records of research achievement, and be able to attract significant extramural research support. The appointee is expected to participate fully in departmental affairs and teaching.

Level of appointment will be commensurate with qualifications and experience. Salary will be based on published UC pay scales. Review of applications will begin **November 1, 2007** and continue until the position is filled. Applications should comprise a single .pdf file containing a CV, copies of recent publications, and statements of research and teaching interests. The application and three letters of reference (sent directly by the referees) should be sent to **ebe-ecol-d@ucsd.edu** with EBE Ecology as the subject line. Applicants are welcome to include in their cover letters a personal statement summarizing their contributions to diversity.

UCSD is an EO/AA Employer with a strong institutional commitment to excellence through diversity.

MOLECULAR EVOLUTION

University of California San Diego
Section of Ecology, Behavior and Evolution
Division of Biological Sciences
http://www-biology.ucsd.edu/

We invite applications for a position in molecular evolution. Applications from junior candidates are strongly encouraged although tenured scientists will be considered. Area of scholarship is open. We are particularly interested in candidates working in the areas of genome evolution, functional genomics, the genetics of adaptation, evo-devo, microbial evolution, and computational biology. We seek candidates who will complement our existing strengths in molecular evolution and who will make connections to other areas of research strength at UCSD such as the Venter Institute. Applicants should demonstrate outstanding records of research achievement, and be able to attract significant extramural research support. The appointee is expected to participate fully in departmental affairs and teaching.

Level of appointment will be commensurate with qualifications and experience. Salary will be based on published UC pay scales. Review of applications will begin **November 1, 2007** and will continue until the position is filled. Applications should comprise a single .pdf file containing a CV, copies of recent publications, and statements of research and teaching interests. The application and three letters of reference (sent directly by the referees) should be sent to **ebe-ev-d@ucsd.edu** with EBE Molecular Evolution as the subject line. Applicants are welcome to include in their cover letters a personal statement summarizing their contributions to diversity.

UCSD is an EO/AA Employer with a strong institutional commitment to excellence through diversity.

THE UNIVERSITY OF CALIFORNIA, SAN DIEGO DIVISION OF BIOLOGICAL SCIENCES

The Division of Biological Sciences at UCSD has a large faculty spanning many areas of biology and one of the largest and most diverse graduate programs in the country. We invite applications for faculty positions in the

NEUROBIOLOGY SECTION

We plan to make appointments in tenure-track or tenured positions at the Assistant, Associate, or Full Professor levels in several areas of neurobiology, particularly systems, computational, and behavioral neurobiology. Applicants must have demonstrated ability to develop a rigorous research program. All applicants must have Ph.D. or equivalent degree and a commitment to teaching at the undergraduate and graduate levels. The level of appointment will be commensurate with qualifications and experience with salary based on the published UC pay scale.

Applications received by **November 1, 2007** will be assured of consideration, and the position will remain open until the positions are filled. Applications should comprise a single .pdf file containing a CV, copies of recent publications, statements of research and teaching interests, and the names of at least three references with mail addresses, email addresses, phone and fax numbers to: **nsearch-c@biomail.ucsd.edu** with Neurobiology as the subject line.

UCSD is an Equal Opportunity-Affirmative Action Employer with a strong institutional commitment to the achievement of diversity among its faculty and staff; and applicants are also invited to summarize their own contributions to diversity.

Faculty Position
The University of California at San Diego
Section of Cell and Developmental Biology
Division of Biological Sciences
http://biology.ucsd.edu/

The Section of Cell and Developmental Biology in the Division of Biological Sciences at UCSD invites applications for a new faculty position with a strong preference for the rank of Assistant Professor. Candidates pursuing innovative research in areas of developmental and cellular biology are encouraged to apply. The successful candidate is expected to have a broad interest in development and cell biology and to complement existing strengths in the Section and the Division. The primary criteria for selection will be excellence and creativity in research and scholarship. All candidates must have a Ph.D., M.D., or an equivalent degree. The successful candidate is expected to participate in the undergraduate and graduate teaching curriculum. Level of appointment will be commensurate with qualifications and experience. Salary will be based upon University of California pay scale.

Complete applications received by **December 3, 2007** will be assured of consideration. A complete application will consist of a curriculum vitae, including a complete list of publications, a short statement of research interests and scientific goals from the applicant, and three letters of recommendation (sent directly by the referees) to: **Development and Cell Biology Search Committee, Division of Biological Sciences, Attn: Sarah Hosford - Mail Code 0116-D, Muir Biology Building, Room 1202, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0116.** Applicants are welcome to include in their cover letters a personal statement summarizing leadership efforts and/or contributions to diversity.

UCSD is an Equal Opportunity-Affirmative Action Employer with a strong institutional commitment to the achievement of diversity among its faculty and staff.

YALE UNIVERSITY
School of Forestry and Environmental Studies
Faculty Position
Terrestrial Ecosystem Ecology

Yale University's School of Forestry and Environmental Studies seeks to hire a tenure track or tenured faculty member in Terrestrial Ecosystem Ecology. Senior candidates will have developed a highly regarded field-oriented research program, have a demonstrated capacity for interdisciplinary research, and possess a very strong record of publication. Junior candidates will have shown the potential for developing such a research program, with a record of publishing, and a demonstrated enthusiasm for interdisciplinary and applied research. He or she will have broad knowledge of terrestrial ecosystem ecology. Subject areas of interest are broad, but examples are: plant-water-soil dynamics, soil biogeochemistry, plant diversity-soil interactions and soil ecology/microbial ecology. Candidates with strong field skills and demonstrated experimental research that scale across systems and/or is comparative are preferred. Candidates should be prepared to teach graduate-level courses on soils and ecosystem ecology, as well as advanced seminars on more specialized topics.

Applicants should send by **15 November 2007** their curriculum vitae, a statement of their research and teaching interests, a list of three references, and representative examples of their publications to:

Terrestrial Ecosystem Ecology Search Committee
c/o Assistant Dean Jane Coppock
Yale School of Forestry and Environmental Studies
205 Prospect Street, New Haven, CT 06511
USA

Or by email to: **jane.coppock@yale.edu**

Additional information on this position may be obtained by contacting **Professor Mark Ashton, 205 Prospect Street, New Haven, CT 06511, USA, phone: (203) 432-9835, email: mark.ashton@yale.edu.**

Yale University is an Affirmative Action /Equal Opportunity Employer. Members of minority groups and women are encouraged to apply.

The University of Texas at Austin

ASSISTANT PROFESSOR in Virology

The Section of Molecular Genetics and Microbiology at the University of Texas at Austin invites applicants for a tenure-track faculty position in virology at the Assistant Professor level. Outstanding applicants at the rank of Associate or Full Professor will also be considered. The Section has a scientifically diverse faculty and all areas will be considered. We are most interested in outstanding candidates studying the molecular biology of animal viruses, particularly viral gene expression and virus-host interactions, including host innate immune responses. We seek an outstanding investigator who will build an active research program and will teach effectively at the undergraduate and graduate levels. The successful candidate will be eligible for membership in the Institute for Cellular and Molecular Biology, will have access to its extensive core facilities, and will have the opportunity to participate in several graduate programs. The position offers excellent start-up funds, salary and laboratory space in a new building that is part of a dynamic, highly interactive research environment.

Please send a single PDF file containing your curriculum vitae, summary of research interests, and names of three references before January 1, 2008 to: mgm_search@biosci.utexas.edu. References may also send their letters directly to the same email address.

Homepages • http://www.biosci.utexas.edu/mgm/
http://www.icmb.utexas.edu

The University of Texas at Austin is an Equal Opportunity Employer
Qualified women and minorities are encouraged to apply
a background check will be conducted on the applicant selected.

Department of the Army
U.S. Army Medical Research and Materiel Command
U.S. Army Medical Research Institute of Infectious Diseases

Electron Microscopist

The Pathology Division of the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), the Department of Defense's premier research Institute for medical defense against biological threats located at Fort Detrick, Maryland, is seeking to fill the position of Electron Microscopist. The selected individual will be involved in the planning and technical management of electron microscopy portions of USAMRIID studies and in the interpretation of ultrastructural changes in study materials at the cellular and tissue levels.

Desired Qualifications: An MD, DVM, PhD, or related degree in the biological sciences and 3 or more years of relevant experience in electron microscopy involving animal or human tissues is required. A successful candidate must demonstrate the ability to provide expertise in the planning and execution of electron microscopy methodologies and the ability to interpret normal and abnormal ultrastructural tissue and cellular changes related to a variety of conditions. The candidate must have excellent written and oral communication skills, strong project management skills, and the ability to work cooperatively in a collaborative, cross- functional team environment.

Interested applicants should refer to announcement **NEBB07164156** or **NEBB07164156D** at **www.cpol.army.mil** for the job vacancy announcement.

Applications will be accepted from **September 28, 2007** to **October 29, 2007**.

THE COMMONWEALTH MEDICAL COLLEGE*

Founding Faculty: Master Teachers and Researchers
Assistant Professors – Associate Professors – Full Professors

The Commonwealth Medical College, a new independent medical school in Pennsylvania is searching for a founding basic science faculty who want to practice state of the art teaching and engage in research in a collaborative setting. This is a chance for faculty to help shape the future of a new, innovative model of medical education. The Commonwealth Medical College will train in a community based, distributive model working with clinical faculty throughout north central and northeastern Pennsylvania, linked by state of the art technology. We are in the accreditation process with LCME and the Pennsylvania Department of Education and hope to accept our first class in 2009. We are funded by state dollars and a generous grant from Blue Cross of Northeastern Pennsylvania. The school enjoys tremendous regional support for its mission of education, research and service and has developed relationships with outstanding local colleges, universities, hospitals and physicians to create a new model of medical education.

We are looking for exceptional faculty in pathology and all basic science areas – biochemistry, physiology, microbiology, and anatomy, who are passionate about teaching and research, interested in mentoring students, and want to participate in an interdisciplinary, collaborative model. We are also seeking faculty who want to build something new, who are comfortable with technology and new teaching methods.

We are interested in scientists who want to grow and develop their research in a new academic model. Our initial interests are in genomics, pharmacogenomics, pharmokinetics (PK) and pharmacodynamics (PD) that are relevant to cancer and epidemiologically important infections and diseases. We are also interested in developing a clinical research center model that would involve community physicians and hospitals and conducting population based studies related to the health needs of the area. Cancer, diabetes, and heart disease are the leading issues of concern, but other areas of expertise are also welcomed.

This is a wonderful opportunity to create something innovative and important and have a significant impact on the future of a new medical school. Unlimited opportunities for growth, both professionally and personally, exist within this collaborative environment. We will be developing curriculum, as well as new facilities, with faculty input.

Please submit your curriculum vitae to: Robert M. D'Alessandri, MD, Dean, The Commonwealth Medical College, 150 North Washington Avenue, Scranton, PA 18503 or electronically to RMD@nepamedc.org.

thecommonwealthmedical.com | The link to the Dean's blog is newmedicalschool.blogspot.com

**This school is proposed and in development phase. Not yet granted degree granting authority from the Pennsylvania Department of Education.*

DANA-FARBER CANCER INSTITUTE

Dedicated to Discovery...Committed to Care.

ASSISTANT PROFESSOR
Tenure Track

Neurobiology/Oncology

The Dana-Farber Cancer Institute has launched a new program on low-grade astrocytomas and related brain tumors in children. Dana-Farber now seeks well-qualified applicants for a tenure-track position at the Assistant or Associate Professor level, with appointment in the Department of Neurobiology at Harvard Medical School or Pediatric Oncology at Children's Hospital, as appropriate. Candidates are expected to direct innovative and independent research on fundamental problems that underlie pediatric brain tumors and to participate in the teaching missions of the Institute and of Harvard Medical School. Developmental neurobiology and neuropathology are two areas of focus for the search. The position offers an attractive start-up support package in a stimulating scientific environment. Applicants must hold a Ph.D., M.D./Ph.D. or M.D. degree, have completed post doctoral training, and have a strong record of research accomplishments. Applications from women and minority candidates are encouraged.

Applicants should submit a curriculum vitae including a full list of publications, a brief statement of previous contributions and future research plans as well as the names and contact information of four references to:

Faculty Search Committee
c/o Deborah Goff
Dana-Farber Cancer Institute
Room SM1068, 44 Binney Street, Boston, MA 02115
E-mail: deborah_goff@dfci.harvard.edu

HARVARD MEDICAL SCHOOL

Applications must be received by November 1, 2007

The Dana-Farber Cancer Institute is an Equal Opportunity Employer.

SHARE THE VISION. FIND THE CURE

HW

Hauptman-Woodward Medical Research Institute
Chief Executive Officer/Scientific Director

The Hauptman-Woodward Medical Research Institute (HWI) is an independent, not-for-profit, biomedical research facility located in the heart of downtown Buffalo's medical campus. For half a century, HWI scientists have been committed to improving human health through study, at a molecular level, of the causes and potential cures of many diseases.

The medical campus is shared by the University at Buffalo and Roswell Park Cancer Institute which, along with Hauptman-Woodward, form the Buffalo Life Sciences Complex. Hauptman-Woodward faculty have added to the cooperative relationship by serving as the University at Buffalo Department of Structural Biology.

A search for a new CEO/Scientific Director has begun as HWI is strategically set for major growth and expansion. The Institute occupies a beautiful, brand new 72,000 square foot state of the art building at the center of the Buffalo Niagara Medical Campus (BNMC). A successfully funded scientist with strong managerial skills will be needed to meet the challenges and opportunities facing HWI. The ability to build endowment funds, as well as the general development efforts, will be required.

For more information about current research programs and the new facility, visit our web site **http://www.hwi.buffalo.edu**. Interested applicants should submit a cover letter and curriculum vitae in strict confidence to:

Eileen P. Blake, Principal
Alexander, Wollman & Stark
epblake2001@yahoo.com or fax to 610.399.5285

The Hauptman-Woodward Institute is an Equal Opportunity Employer

POSITIONS OPEN

ASSOCIATE PROFESSOR
in an Area of Infectious Disease

The Department of Biological Sciences at the University of Notre Dame invites applications at the Associate Professor level. The candidate should have a Ph.D. or equivalent and a demonstrated record of research and teaching accomplishments. He/she is expected to have an outstanding research program in the general area of infectious disease with a strong track record of publications and extramural funding. The candidate's research should complement the infectious disease focus within the Department and the College of Science. Individuals whose program has cross-disciplinary components are particularly encouraged to apply. The successful candidate will be expected to teach an undergraduate and a graduate course. The new faculty member will be part of the Center for Global Health and Infectious Diseases with opportunities for collaborations with other interdisciplinary centers within the University, including the Keck Center for Transgene Research, and the Interdisciplinary Center for the Study of Biocomplexity. The Department also holds an NSF-Integrative Graduate Education and Research Traineeship training grant. Excellent cores including new genomics, imaging and BSL 3 containment facilities are available. The position offers an attractive salary, startup package, and laboratory space. Additional information on the Department, its faculty, and facilities is available at **website: http://biology.nd.edu.** Applications will be accepted until December 1, 2007, but review will commence immediately. Qualified individuals should send their curriculum vitae, the names and addresses of at least three references, and a summary of current research and teaching interests to: **Chair, Infectious Disease Search Committee, Department of Biological Sciences, University of Notre Dame, Notre Dame, IN 46556-0369.** For more information, e-mail the **Search Chair** at **e-mail:schorey.1@nd.edu.**

The University of Notre Dame is an Affirmative Action/Equal Opportunity Employer. Women and minority candidates are encouraged to apply.

ASSISTANT/ASSOCIATE PROFESSOR
Bacteriology

The Department of Microbiology and Immunology at the Brody School of Medicine, East Carolina University (ECU), invites applications for a tenure-track faculty position at the Assistant Professor or Associate Professor level. We are seeking an individual to develop an independent, funded research program using molecular approaches in the area of bacterial pathogenesis related to human health and disease. The successful candidate also will be expected to participate in teaching medical and graduate students. Salary and rank will be commensurate with qualifications. Appointment at the Associate Professor level requires a strong record of continuous research funding including current extramural support and evidence of successful teaching performance. The Department has 13 full-time tenure-track faculty, an active doctoral studies program, and is fully equipped with state-of-the-art instrumentation. Onsite facilities include those for flow cytometry, confocal microscopy, laser capture microdissection, phosphoimaging, and electron microscopy. In addition, the School of Medicine has a new modern accredited animal care facility with a well-trained veterinary staff. ECU is located in Greenville, North Carolina, a small city with a population of 70,000, approximately 90 miles east of Raleigh and a short ride from the Crystal Coast beaches and the Outer Banks. Applicants should apply online at **website: http://www.jobs.ecu.edu** and complete the applicant profile and upload or attach the required documents: curriculum vitae, an outline of their planned research program, and names and complete addresses of three references. Questions pertaining to the position can be addressed to **C. Jeffrey Smith** at **e-mail: smithcha@ecu.edu.** *East Carolina University is an Equal Opportunity/Affirmative Action University. Accommodates individuals with disabilities. Applicants must comply with the Immigration Reform and Control Act.*

POSITIONS OPEN

The University of Georgia

FACULTY POSITION in PHARMACEUTICS and DRUG TRANSPORT

The Department of Pharmaceutical and Biomedical Sciences at the University of Georgia, Athens invites applications for a full-time, tenure-track **ASSISTANT PROFESSOR** position in the general area of pharmaceutics and drug transport. Applicants should possess a Ph.D. or Pharm.D./Ph.D. or equivalent degree with pharmaceutical sciences or a related area as the focus of their graduate education and research training. Excellent communication skills and the ability to teach basic pharmaceutics and drug delivery/drug transport concepts at both the Pharm.D. and Ph.D. levels are required. Each successful applicant is expected to develop a dynamic, extramurally funded research program in the area identified above. To be assured of full consideration, applications should be received by December 1, 2007. Interested qualified applicants should submit a letter of application, curriculum vitae, a research plan and three confidential letters of recommendation to: **Chair, Search Committee, Department of Pharmaceutical and Biomedical Sciences (Job Code: AP/54679), R. C. Wilson Pharmacy Building, University of Georgia, Athens, GA 30602-2352.** Applicants may also apply online to e-mail: pbssearch@rx.uga.edu. Note: Job Code must be posted on curriculum vitae/application for consideration. *The University of Georgia is an Equal Employment Opportunity/Affirmative Action Employer. Applications from qualified women and minority candidates are encouraged.*

ORGANIC CHEMISTRY
University of Southern California

The Department of Chemistry of the University of Southern California invites applications for a tenure-track faculty position in organic chemistry, to start in the fall of 2008. Candidates for the rank of **ASSISTANT or ASSOCIATE PROFESSOR** will be considered, depending on experience and qualifications. A Ph.D. degree in chemistry is required. We are interested in candidates with research interests in all areas of experimental organic chemistry, particularly in the fields of chemical synthesis, hydrocarbon chemistry, electrochemistry, or catalysis, with an emphasis on energy and materials research. Evidence of research accomplishments and potential as a scholar and dedicated teacher is important. Interested candidates should submit their curriculum vitae, a description of research plans and teaching interests, and arrange to send three letters of recommendation to: **Professor Nicos A. Petasis, Organic Chemistry Search Committee, Department of Chemistry and Loker Hydrocarbon Research Institute, College of Letters, Arts and Sciences, University of Southern California, 837 Bloom Walk, Los Angeles, CA 90089-1661.** Applications will be considered beginning October 25, 2007, and until the position is filled. *USC values diversity and is committed to Equal Opportunity in employment. Women and men, and members of all racial and ethnic groups are encouraged to apply.*

GRADUATE PROGRAM

Engineering and Public Policy at Carnegie Mellon seeks **DOCTORAL STUDENTS** with technical backgrounds to address policy issues in electric power, energy and environmental issues, climate change; information and telecom policy; risk analysis and regulation; management of innovation and R&D, et cetera. See **website: http://www.epp.cmu.edu. Victoria Finney, Engineering and Public Policy, Carnegie Mellon, Pittsburgh, PA 15213 U.S.A.**

POSITIONS OPEN

BIOLOGY (ECOLOGY). Whitman College announces a tenure-track position in biology, at the rank of **ASSISTANT PROFESSOR,** effective 2008-2009. Ph.D. required, postdoctoral experience preferred. We seek a **FIELD BIOLOGIST** with expertise in ecology whose teaching/research interests consider ecological phenomena (such as animal behavior or interactions) in evolutionary contexts. Teaching duties will include courses and laboratories in ecology and field biology, contributions to Whitman's interdisciplinary environmental studies program, and supervision of student research in biology. Whitman College wishes to reinforce its commitment to enhance diversity, broadly defined, recognizing that to provide a diverse learning environment is to prepare students for personal and professional success in an increasingly multicultural and global society. In their application, candidates are strongly encouraged to address their potential contribution to the promotion of diversity, a core value of the Whitman College community; their interest in working with undergraduates as teachers and scholars in a liberal arts environment that emphasizes close student-faculty interaction; and their interest in participating in the College's general education offerings. Deadline: October 19, 2007. Materials should include a letter of application; curriculum vitae; three letters of reference; undergraduate and graduate transcripts; teaching evaluations or other evidence of demonstrated or potential excellence in undergraduate instruction; and separate statements on the candidate's teaching interests and scholarly agenda.

Send to: **Patti Moss, Biology Department, Whitman College, 345 Boyer Avenue, Walla Walla, WA 99362.** Whitman College, located in the scenic Columbia Basin, is a small, selective, liberal arts college dedicated to providing excellent educational opportunities for students. The College has a generous sabbatical leave program and professional development support for both research and teaching. For additional information about Whitman College and the Walla Walla area, see **websites: http://www.whitman.edu** and **http://www.wallawalla.org.** *No applicant shall be discriminated against on the basis of race, national or ethnic origin, age, gender, sexual orientation, marital status, religion, creed, or disability.*

FACULTY POSITION in ECOLOGY

The University of North Carolina at Chapel Hill's Department of Biology **(website: http://www.bio.unc.edu/)** invites applications for a tenure-track position in ecology. The position is at the rank of **ASSISTANT PROFESSOR,** effective on or after July 1, 2008. Applicants must have a Ph.D. and active research program in some aspect of the ecological sciences. Application via e-mail **(e-mail: ecosearch07@bio.unc.edu)** is preferred, with cover letter, curriculum vitae, and research and teaching statements submitted as a single PDF file; up to three (PDF) reprints; and four letters of reference (e-mail plus hard copy) addressed to: **Dr. Joel Kingsolver, Chair, Ecologist Search Committee, Department of Biology, CB#3280, Coker Hall, University of North Carolina-CH, Chapel Hill, NC 27599-3280.** Closing date: until filled; review of applications begins November 16, 2007. *The University of North Carolina is an Equal Opportunity Employer.*

POSTDOCTORAL POSITION available at University of Texas Medical Branch, Galveston, Texas. An NIH-funded Postdoctoral position is available immediately to study the role of γ-secretase in growth factor signaling during pathological angiogenesis (see: *J. Biol. Chem.* **281**:3604-13, 2006). The applicant should have a strong background in vascular/endothelial biology and experience in studying intracellular signaling pathways. Experience with cell culture and protein analysis is essential. A Ph.D. and/or an M.D. is required. Salary and benefits will be commensurate with experience and in accordance with NIH guidelines. Interested individuals should send a cover letter, curriculum vitae, and contact information for three references to: **Michael E. Boulton, Department of Ophthalmology and Visual Sciences, 301 University Boulevard, Galveston, TX 77555-1106. E-mail: meboulto@utmb.edu.** *An Equal Opportunity Institution.*

Washington University in St. Louis
SCHOOL OF MEDICINE

Faculty Position in Single Molecule Studies

The DEPARTMENT OF BIOCHEMISTRY AND MOLECULAR BIOPHYSICS at Washington University School of Medicine invites applications for a tenure-track or tenured faculty position with a research focus in the area of single molecule approaches to study enzyme mechanisms and/or interacting macromolecular systems. Applicants at the Assistant, Associate, or Full Professor level will be considered. The successful candidate will conduct independent research within a growing department that is broadly represented in quantitative studies of macromolecules, including enzymology, molecular interactions and dynamics, structural and computational biology (**http://www.biochem.wustl.edu**). Enthusiasm for teaching and mentoring young scientists is also important.

Washington University has a highly interactive research environment with vigorous interdisciplinary graduate and medical scientist training programs. Minority and women scientists are especially encouraged to apply. Applicants should submit their curriculum vitae, selected reprints, a short summary of future research plans and the names of references electronically to **single-molecule-search@biochem.wustl.edu**, or else by mail to:

SINGLE MOLECULE SEARCH
Tom Ellenberger, Raymond H. Wittcoff Professor and Head
Department of Biochemistry and Molecular Biophysics, Box 8231
Washington University School of Medicine
660 S. Euclid Ave.
St. Louis, MO 63110

AN EQUAL OPPORTUNITY EMPLOYER.

Department of Geosciences
PRINCETON UNIVERSITY

The Department of Geosciences at Princeton University is seeking applications for a tenured faculty position in **solid-earth geophysics**. We are particularly interested in individuals who could interact productively with current members of the department, in areas including but not limited to seismology, geodynamics, and mineral physics.

Applicants should send a curriculum vitae, including a publications list, a statement of research and teaching interests, and contact information for three references to: **Allan Rubin, Search Committee Chair, Department of Geosciences, Guyot Hall, Princeton University, Princeton, NJ 08544**. The starting date is flexible. Evaluation of applications will begin immediately; interviews of candidates will begin in the fall of 2007 and will continue until the position is filled.

For general information about applying to Princeton and how to self-identify, please link to **http://web.princeton.edu/sites/dof/ApplicantsInfo.htm**.

Princeton University is an Equal Opportunity Employer and complies with applicable EEO and Affirmative Action regulations.

Assistant Scientist/Extension Specialist E-2 in Agro-Meteorology

Washington Agricultural Weather Network
Position #101008E/101009R
Search #4541

Assistant Scientist/Extension Specialist E-2 in Agro-Meteorology: Washington State University's (WSU) newly created Agricultural Weather Network (AgWeatherNet) seeks applicants for a permanent, 12-month, tenure-track faculty position, 40% Agricultural Research Center and 60% WSU Extension in Agro-Meteorology. The position is located on the WSU Irrigated Agriculture Research and Extension Center (IAREC) Prosser, WA. This position is the lead extension specialist/research scientist for the WSU AgWeatherNet Team. The successful candidate will be expected to provide leadership in the area of meteorology and its interaction with agriculture. The successful applicant will be expected to conduct an approved program of research consistent with the mission of the Agricultural Research Center. Possible areas of research include interrelationships between weather and crop production, plant, insect and disease development, pest treatment modeling, soil water content, irrigation scheduling, soil erosion, soil fertility and plant nutrient movement, effect of wind patterns on pheromone concentration within an area, or water balance. The candidate's home department will be flexible to reflect the successful candidate's discipline (Biosystems Engineering, Crop and Soil Sciences, Entomology, Horticulture, Plant Pathology or other related department). A demonstrated ability to develop extension programming, conduct research, and disseminate the results in leading academic journals and extension type publications is essential. Superior written and verbal communication skills are critical. The ability to work collaboratively with a wide range of research scientists from different disciplines and with extension educators from agriculture is essential.

Required: Earned Ph.D. at the time of hire in agricultural meteorology or related field, with documented experience in agricultural meteorology as it relates to agro-ecosystem, crop, insect, and/or disease modeling or forecasting.

Desired: Record of publishing in peer-reviewed scientific journals, demonstrated outreach activities and interaction with client groups, record of successful participation on multidisciplinary teams, demonstrated ability to communicate effectively both orally and in writing, demonstrated ability to conduct publishable applied research and secure extramural funding, demonstrated ability to develop and work with other extension educators in conducting educational and field demonstration programs, and demonstrated ability in program, budget, and personnel management. Salary is competitive and commensurate with qualifications and experience.

Application: Letter of application addressing qualifications for the position, a current curriculum vitae, official transcripts, and arrange for three letters of reference (direct from source), which explicitly address the qualifications. Send to: **Dr. Gary Grove, Washington State University, 24106 N Bunn Rd., Prosser, WA 99350-8694; grove@wsu.edu, 509-786-9283 voice, 509-786-9370 FAX**. Screening: **15 January 2008**.

Washington State University is an Equal Opportunity/Affirmative Action Educator and Employer. Women, ethnic minorities, Vietnam-era or disabled veterans, persons of disability and/or persons age 40 and over are encouraged to apply.

POSITIONS OPEN

ASSISTANT/ASSOCIATE/FULL PROFESSOR (SYSTEMS PHYSIOLOGIST/TENURE TRACK)
Department of Biological Sciences

The Department of Biological Sciences at Louisiana State University, **website: http://www.biology.lsu.edu,** invites applications for an Assistant/Associate/Full Professor (systems physiology/tenure track) position. Required qualifications: Ph.D. or equivalent degree in biological sciences or a related field; postdoctoral experience and a record of creative and significant research in any area of experimental animal physiology (nonmammalian model systems preferred). Responsibilities: develops a vigorous, extramurally funded research program; contributes to undergraduate and graduate teaching. We encourage applications from women and minorities. Salary and level will be commensurate with experience. An offer of employment is contingent on a satisfactory pre-employment background check. Application deadline is November 1, 2007, or until a candidate is selected. Send curriculum vitae (including e-mail address), statement of research and teaching interests, three letters of recommendation, and reprints of key publications to:

Systems Physiology Search Committee
Department of Biological Sciences
202 Life Sciences Building
Louisiana State University
Reference: #024645
Baton Rouge, LA 70803

LSU is an Equal Opportunity/Equal Access Employer.

Clarkson University invites applications for faculty positions in biochemistry and biological physics. Clarkson offers a highly interdisciplinary and collaborative environment and the successful candidates should have research interests complementary to and compatible with faculty in the Chemistry or Physics Departments and also with our emerging group in bio/nanomaterials. Successful candidates are expected to develop vigorous, creative, externally funded research programs. Applicants must have a doctoral degree in an appropriate field along with postdoctoral experience. They must also have a commitment to teaching at the Ph.D., M.S., and undergraduate levels. Please submit curriculum vitae, statements of research and teaching interests, and reference letters from at least three references, to the: **Search Committee Chair, Department of Chemistry (Job #23-06) or Department of Physics (Job #42-06), Clarkson University, 8 Clarkson Avenue, Potsdam, NY 13699-5810.** Please reference the job number in your letter. Review of applications will begin immediately and continue until the positions are filled. Preference will be given for candidates at the **ASSISTANT PROFESSOR** level, to begin in the fall semester of 2008. *Clarkson University is an Equal Opportunity/Affirmative Action Employer; applications from women and minorities are strongly encouraged.*

ASSISTANT PROFESSOR
Kansas State University
Molecular and Cellular Biology

A tenure-track Assistant Professor position is available in the division of biology in the general area of molecular and cellular biology. The successful candidate will establish an outstanding, extramurally funded research program and will also contribute to graduate and undergraduate instruction to a diverse population. A Ph.D. or equivalent and postdoctoral training are required. The position includes a competitive salary and startup package. For more information go to **website: http://www.ksu.edu/biology/bio/news.htm.** Applications should be sent to: **Dr. Rollie Clem, Chair, Molecular and Cellular Biology Search Committee, Division of Biology, 116 Ackert Hall, Kansas State University, Manhattan, KS 66506-4901. E-mail: rclem@ksu.edu.** Review of applications will begin November 1, 2007, and continue until the position is filled. *KSU is an Equal Opportunity/Affirmative Action Employer, and actively seeks diversity among its employees.*

POSITIONS OPEN

The University of Georgia

FACULTY POSITION in PHARMACEUTICAL SCIENCES

The Department of Pharmaceutical and Biomedical Sciences at the University of Georgia, Athens, invites applications for a full-time, tenure-track faculty position as **ASSISTANT or ASSOCIATE PROFESSOR** in the area of pharmaceutical sciences (biopharmaceutics/biopharmaceutical engineering or pharmacology/molecular disease targets). Applicants should possess a Ph.D. or Pharm.D./Ph.D. or equivalent degree with pharmaceutical sciences or pharmacology as the focus of their graduate education and research training. Excellent communication skills and the ability to teach at both the Pharm.D. and Ph.D. levels are required. Each successful applicant is expected to have or to develop a dynamic, extramurally funded research program in an area identified above. To be assured of full consideration, applications should be received by January 1, 2008. Interested qualified applicants should submit a letter of application, curriculum vitae, a research plan and three confidential letters of recommendation to: **Chair, Search Committee (Job Code: A-AP/52334), Department of Pharmaceutical and Biomedical Sciences, R. C. Wilson Pharmacy Building, University of Georgia, Athens, GA 30602-2352.** Applicants may also apply online to **e-mail: pbssearch@rx.uga.edu.** Note: Job Code must be posted on curriculum vitae/application for consideration. *The University of Georgia is an Equal Employment Opportunity/Affirmative Action Employer. Applications from qualified women and minority candidates are encouraged.*

DEPARTMENT of STRUCTURAL and CELLULAR BIOLOGY FACULTY POSITION

The Department of Structural and Cellular Biology is seeking applications of all qualified candidates for a position (at the **ASSISTANT PROFESSOR to PROFESSOR LEVEL**) as the **DIRECTOR** of the medical neuroscience course. This individual would direct the medical neuroscience course and assist in teaching gross anatomy. Candidates must have an earned Doctorate (Ph.D. or M.D.). Prior experience in teaching of medical neuroscience is absolutely essential and experience in gross anatomy is also desirable. Extramural research funding is not required; however, candidates with extramurally funded research programs in either cancer biology or neuroscience are of particular interest. The Department is undergoing major expansion, and appropriate startup funds will be provided along with excellent facilities and environment. Applicants should submit a cover letter, curriculum vitae, summary of teaching experiences and philosophies, if applicable, a summary of research interests and plans and funding history, and letters of references to: **Dr. Steven M. Hill, Professor and Chair, Department of Structural and Cellular Biology, SL49, Tulane University Health Sciences Center, School of Medicine, 1430 Tulane Avenue, New Orleans, LA 70112** by November 1, 2007. *Tulane University is an Affirmative Action/Equal Opportunity Employer. Women and minorities are encouraged to apply.*

The Division of Public Health Sciences of the Fred Hutchinson Cancer Research Center invites applications from laboratory-based scientists with an interest in molecular diagnostics, including but not limited to aspects of predictive medicine, early detection, diagnosis, treatment response, and risk assessment.

Further information is available at **website: http://www.fhcrc.org/about/jobs/** and selecting job posting identification # KW-21205.

POSITIONS OPEN

TENURE-TRACK POSITION
Evolution of Complex Phenotypes

Tenure-track faculty position available in the School of Biological Sciences, University of Nebraska at **ASSISTANT PROFESSOR** level, for a person conducting integrative, functional studies on the evolution of complex phenotypes. Research focus should be primarily experimental, although a theoretical component would be welcome. Research on any taxon and level of biological organization, using any approaches. Examples include, but are not limited to, molecular, quantitative-genetic, endocrine, biochemical neurophysiological, and/or systems/genomic approaches to metabolic or cell signaling networks, interactions among cells or organs, or systemic regulators that underlie intraspecific variation in developmental, biochemical, behavioral, or life-history components of complex phenotypes. This position is part of a developing research cluster in integrative and systems biology at the University of Nebraska. The successful candidate will also be involved in undergraduate and graduate teaching in area of expertise. Applications will be considered until November 5, 2007, or until a suitable candidate is found. A Ph.D. in the life sciences is required and postdoctoral experience is preferred.

Start date January 2009; the position will remain open until a suitable candidate is selected.

To apply, log on to **website: http://employment.unl.edu,** requisition #070765, and complete the faculty/administrative information form and attach curriculum vitae; cover letter; statement of research interests and teaching interests and philosophy; representative publications; and names, addresses, and telephone numbers of three references. Arrange for three letters of reference to be sent by November 5, 2007, to: **Dr. Alan Kamil, School of Biological Sciences, University of Nebraska-Lincoln, 348 Manter Hall, Lincoln, NE 68588-0118.**

UNL is committed to a pluralistic campus community through Affirmative Action and Equal Opportunity, and is responsive to the needs of dual-career couples. We assure responsible accommodation under the Americans with Disabilities Act; for assistance contact ***Dr. Alan Kamil*** *at* ***telephone: 402-472-6676.***

ECOLOGICAL MODELER

The Biology Department at Georgia Southern University seeks to fill a tenure-track faculty position in the area of ecological modeling or landscape ecology. The required qualifications for this position includes a Ph.D. in biological sciences, demonstrated excellence in research, potential to obtain external funding, ability to contribute to the Department's research strengths, and a demonstrated commitment to excellence in teaching and professional service. Postdoctoral experience and a research program that incorporates geographic information system, global positioning system, and remote sensing are preferred. The starting date is August 1, 2008. The postmark deadline for receipt of applications is October 31, 2007. Information about the Department and faculty, full description of preferred and required qualifications, and application instructions can be located at **websites: http://www.georgiasouthern.edu** and **http://cost.georgiasouthern.edu/biology.** Finalists will be required to submit to a background investigation. *Georgia Southern is an open records state; Affirmative Action/Equal Opportunity Affirmative Action/Equal Opportunity Institution. Individuals who need reasonable accommodations under the ADA should contact the appropriate Search Chair.*

Position: **CHIEF PROJECT SCIENTIST.** Living Oceans Foundation, Washington, D.C., 501(c)(3) Private Operating Foundation. See **website: http://www.livingoceansfoundation.org** for full job description. Send resume by November 15, 2007. Seeking experienced Ph.D. with coral reef ecology research skills and scientific diving certification. *U.S. citizen or current U.S. resident.* Contact **Executive Director, e-mail: prenaud@livingoceansfoundation.org, telephone: 301-577-1288.**

Directorship of the Ras al Khaimah Centre for Advanced Materials

The new Ras al Khaimah Centre for Advanced Materials (RAK-CAM) will be established in the United Arab Emirates in Fall 2007 under the Patronage of His Highness Sheik Saud bin Saqr al Qasimi. The centre will fill multiple ambitious roles for the Emirate:

i become a flagship for advanced materials research in the Middle East.
ii provide educational and training opportunities for aspiring scientists and engineers from the Emirate and the region as a whole.
iii carry out research in support of local industries.
iv spawn new business opportunities in the form of start-up companies.
v create new options to ensure energy security and sustainable development in Ras al Khaimah

The scope of RAK-CAM will embrace interdisciplinary materials science in the broadest sense, from structural materials to advanced electronic materials and biomaterials. In the first instance, RAK-CAM will comprise a Director, an Associate Director, 8 research scientists, and several visiting professors. These will be supported by a permanent technical and administrative staff as well as short-term (3 year) post-doctoral researchers and graduate students. A state-of-the-art 6000m2 building is currently being designed, and construction is expected to commence in late 2007. The research topics pursued in the Centre will include many of the following areas:

- Advanced structural materials, ceramics and composites
- Polymeric materials (including plastic and molecular electronics)
- Inorganic materials, e.g. minerals and novel synthetic inorganics
- Electronic materials, e.g. compound semiconductors, solid state lighting
- Nanomaterials for diverse applications
- Biomaterials, e.g. materials for biofuel technologies
- Materials for solar energy applications
- Energy storage systems, including rechargeable batteries and supercapacitors
- Materials for environmental remediation and hydrocarbon processing, e.g. catalysis and separations
- Materials for water purification and conservation technologies

RAK-CAM is seeking a Director with a distinguished track record in the broad materials science area in either academia, industry or a national laboratory. He will also have extensive experience in administration and leadership. The specific duties of the Director will include playing a central role in recruiting the research staff for RAK-CAM, selecting and purchasing appropriate equipment for the laboratories, and running an active research program. A search committee comprising Anthony K. Cheetham, Director of the International Center for Materials Research at UC Santa Barbara (Chair), Mildred Dresselhaus, Professor at the Massachusetts Institute of Technology, Richard H. Friend, Professor of Physics at the University of Cambridge, Michael L. Klein, Director of the Laboratory for Research on the Structure of Materials at the University of Pennsylvania, C.N.R. Rao, Linus Pauling Professor at the Jawaharlal Centre for Advanced Scientific Research in Bangalore, and the Hon. Peter Watson, will select the Director.

The Director will receive an internationally competitive salary, tax-free, and a comprehensive benefits package including accommodation, health coverage, an educational allowance for dependents, etc. Further particulars can be obtained from **info@rakcam.org**. Applications, comprising a full resume, list of publications, a 3-page research proposal, and the names and addresses of 3 referees, should be sent electronically to **SearchCommitee@rakcam.org**. The closing date for applications will be October 15, 2007, and short-listed candidates will be called for interview in November or December 2007. The position will be available from January 2008 onwards.

Center for Cell Dynamics Johns Hopkins University

The **Institute for Basic Biomedical Sciences** at **The JHU School of Medicine** has initiated a major initiative to recruit new faculty and create cross-disciplinary and highly interactive research centers.

The **Center for Cell Dynamics** focuses on the analysis of spatially and temporally regulated molecular events in living cells, tissues and organisms. Research within the center focuses on a variety of essential cellular behaviors including cytokinesis, cell motility, and neural plasticity. The Center cuts across traditional departmental boundaries with the common goal of monitoring dynamic biochemical reactions in real time with the highest possible spatial resolution. The Center is recruiting faculty who will develop and apply new experimental approaches in a collaborative, interactive, and interdisciplinary environment. Faculty will reside in new laboratories in the Basic Science research complex and receive primary appointments in existing Departments within the School of Medicine.

Applicants should submit an application by January 15, 2008 via email (IBBScenters@jhmi.edu). Include a CV, research plan, names of three references and up to three publications (all in pdf format). Indicate **CCD** in the subject line.

The Johns Hopkins University is committed to diversity and equality in education and employment and encourages applicants from under-represented groups.

Faculty Position in Chemical Biology

The Life Sciences Institute (LSI) at the University of Michigan invites applications for a position at the rank of Assistant or Associate Professor in the field of chemical biology. Chemical biology is broadly defined and the successful applicant will use chemical methods to address an important biological question.

The LSI is a scientific enterprise at the University of Michigan dedicated to opening new scientific paths by blending diverse research talents in a state-of-the-art collaborative physical space (www.lsi.umich.edu). The LSI is currently home to 26 interactive faculty in the areas of cell biology, genetics, bioinformatics, structural biology, signaling, and chemistry.

Candidates are expected to develop an internationally recognized program of scholarly research and to excel in teaching at undergraduate and graduate levels. The positions will remain open until filled but preference will be given to applicants who have submitted all requested materials prior to **October 15, 2007**. Applicants should send the following (in PDF format): a curriculum vitae, copies of up to three reprints, a one- to two-page summary of research plans, and arrange to have three letters of reference sent directly to: **lsichembio@umich.edu**.

The University of Michigan is supportive of the needs of dual career couples and is a non-discriminatory, Affirmative Action Employer. Women and minorities are encouraged to apply.

life sciences institute

POSITIONS OPEN

INORGANIC FACULTY POSITION
University of California, Los Angeles (UCLA)

The Department of Chemistry and Biochemistry of the University of California, Los Angeles, invites applications for a faculty position in inorganic chemistry at the **ASSISTANT, ASSOCIATE, or FULL PROFESSOR** rank. We are seeking a candidate who will establish a vigorous and innovative research program. Depending on the level, candidates must give evidence of potential or demonstrated distinction in scholarship and teaching. Applications should include curriculum vitae, a statement of research accomplishments and proposed research plans (not exceeding four pages), and reprints of representative publications. Applicants at the Assistant Professor level should also arrange for three letters of recommendation to be mailed to the address below. To assure consideration, all application materials and letters should be received by November 2, 2007, and directed to:

Chair
Inorganic Search Committee
Department of Chemistry and Biochemistry
University of California, Los Angeles
P.O. Box 951569
Los Angeles, CA 90095-1569
Fax: 310-206-8010

UCLA is an Equal Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply.

FACULTY POSITION in MOLECULAR, CELLULAR, and DEVELOPMENTAL BIOLOGY
University of Colorado at Boulder

The Department of Molecular, Cellular, and Developmental Biology invites applications for a tenure-track **ASSISTANT PROFESSOR** in the area of molecular, cellular, or developmental biology. Applicants must have a Ph.D., M.D., or equivalent; and postdoctoral research experience. The candidate is expected to develop a vigorous and innovative research program, and have enthusiasm for teaching at the undergraduate and graduate levels.

Applicants should submit curriculum vitae and a concise statement of research and teaching interests, and arrange to have three reference letters sent to:

Molecular, Cellular, and Developmental Biology
Faculty Search Committee
Department of Molecular, Cellular, and Developmental Biology
University of Colorado at Boulder
347 UCB
Boulder, CO 80309-0347

Review of applications will begin December 1, 2007. Applications will be accepted until the position is filled. See **website: http:// www.Colorado.edu/ArtsSciences/Jobs/** for full job description. *The University of Colorado at Boulder is committed to diversity and equality in education and employment.*

ASSISTANT PROFESSOR, NEUROBIOLOGY. Tenure-track position starting fall 2008. Ph.D., expertise in invertebrate or nonmammalian systems, and application of cellular/molecular techniques required. Must demonstrate aptitude for teaching undergraduates. Postdoctoral experience preferred.

Will teach courses in neurobiology, introductory biology, the University's liberal arts core curriculum, and first-year program. Participation in interdisciplinary Cognitive Neuroscience Program available. Academic advisement, continued professional development, and scholarly activity expected. Send curriculum vitae, all graduate transcripts, statement of teaching philosophy and research interest, documentation of teaching ability, and three current letters of recommendation to: **Dr. Gloria Colurso, Biology Department, Eastern Connecticut State University, Willimantic, CT 06226.**

Search will continue until position is filled. *ECSU is an Affirmative Action/Equal Opportunity Employer.*

POSITIONS OPEN

CAL POLY

SAN LUIS OBISPO, CALIFORNIA 93407

ANIMAL/SYSTEMS PHYSIOLOGIST. The Biological Sciences Department within the College of Science and Mathematics at California Polytechnic State University is seeking a full-time, academic year, tenure-track Animal Physiologist at the **ASSISTANT PROFESSOR** rank beginning September 2008. Teaching responsibilities may include general/cellular physiology as well as vertebrate/human anatomy and physiology at the undergraduate and graduate level and other undergraduate and graduate courses as appropriate to background and training. The position is open to all specialties; desirable research areas include environmental physiology, neurobiology, and systems physiology.

The successful candidate must have a strong commitment to undergraduate and graduate teaching, curriculum development, and implementation of a student-centered research program. Ph.D. in related field required at time of hiring. Postdoctoral research or teaching experience preferred. Salary is commensurate with qualifications and experience.

To apply, visit **website: http://www.calpolyjobs.org,** complete a required online faculty application and submit to requisition #101413; attach your curriculum vitae, statement of teaching philosophy, statement of professional goals, a PDF file of a recent publication or submitted manuscript, and unofficial transcripts. (Official graduate transcripts will be required for appointment.) Arrange to have three letters of recommendation sent to: **Dr. Michael Yoshimura, Chair, Biological Sciences Department, California Polytechnic State University, San Luis Obispo, CA 93407-0401.** Review of applications will begin October 28, 2007. Applications received after this date may be considered. For questions, contact the Biological Sciences Department at **telephone: 805-756-5242.** *Cal Poly is strongly committed to achieving excellence through cultural diversity. The University actively encourages applications and nominations of all qualified individuals. Equal Employment Opportunity.*

The UNIVERSITY of TEXAS SOUTHWESTERN MEDICAL CENTER

ASSISTANT PROFESSORS. The Department of Physiology invites outstanding scientists with Ph.D., M.D., or equivalent degrees to apply for tenure-track Assistant Professor positions. Candidates who use innovative optical, mechanical, electrical, molecular biological, or computational methods with important applications to physiological systems, ranging from individual genes and proteins to cells and organs are encouraged to apply. However, the scientific excellence of the candidates is more important than the specific area of research.

These positions are part of the continuing growth of the Department at one of the country's leading academic medical centers and will be supported by significant laboratory space on our new campus, competitive salaries, and exceptional startup packages. The University of Texas (UT) Southwestern Medical Center is the scientific home to four Nobel Prize Laureates, 17 members of the National Academy of Sciences, and 19 members of the Institute of Medicine. UT Southwestern conducts more than 3,500 research projects annually totaling more than $350 million.

Applicants should submit curriculum vitae, a brief statement of research plans, and arrange to have three letters of reference sent to: **James Stull, Ph.D., c/o Gena McElyea, Department of Physiology, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9040.** *UT Southwestern strongly encourages applications from women, minorities, and people with physical challenges. An Equal Opportunity Employer.*

POSITIONS OPEN

FACULTY POSITION in FUNCTIONAL GENOMICS/SYSTEMS BIOLOGY

As part of a major hiring initiative in genomics and systems biology, the Department of Biology at the University of Rochester **(website: http://www.rochester.edu/College/BIO)** is recruiting a tenure-track faculty member at any level with expertise in functional genomics and/or systems biology.

The successful candidate will address mechanistic problems in biology with a genomics or systems-level perspective. All qualified candidates are welcome to apply; candidates working in the areas of cell or developmental biology and structural, functional, or computational genomics are particularly encouraged.

Candidates with a strong record of accomplishment should submit curriculum vitae, statement of research interests/plans, PDFs of two publications, and arrange to have three letters of recommendation sent to **e-mail: gensys@rochester.edu.**

Please indicate that the application is intended for position number one. Review of applications will start October 15, 2007.

The University of Rochester is an Equal Opportunity Employer, has a strong commitment to diversity and actively encourages applications from candidates from groups underrepresented in higher education.

FACULTY POSITION in EVOLUTIONARY/ COMPARATIVE GENOMICS
ASSISTANT/ASSOCIATE PROFESSOR of BIOLOGY

The Department of Biology at the University of Rochester invites applications for a tenure-track faculty position in evolutionary/comparative genomics. This is one of four new faculty positions in genomics to be filled this year as part of an interdepartmental Initiative in Genomics and Systems Biology. The successful candidate will benefit from the Department's strengths in evolutionary genetics, a multidisciplinary research community, and state-of-the-art infrastructure and core facilities at the University of Rochester.

Candidates with a strong record of accomplishment should submit curriculum vitae, statement of research interests/plans, PDFs of two publications, and arrange to have three letters of recommendation sent to **e-mail: gensys@rochester.edu.** Please indicate that the application is intended for position number two. Review of applications will start October 15, 2007. *The University of Rochester is an Equal Opportunity Employer, has a strong commitment to diversity and actively encourages applications from candidates from groups underrepresented in higher education.*

Minnesota State University, Mankato, seeks an energetic and dynamic leader for the position of **DEAN, COLLEGE of SCIENCE, ENGINEERING and TECHNOLOGY.**

The Dean is the Chief Administrator and Executive Officer who provides vision and leadership for the College and reports directly to the Provost and Vice President for Academic Affairs. The Dean is responsible for academic and administrative planning; and oversees ten departments and five applied research centers; program reviews and external accreditations; budgeting; administration of collective bargaining agreements; implementation of college and university policies; promoting, developing and encouraging diversity and Affirmative Action initiatives; recruitment, development and evaluation of faculty; student relations; fundraising and grant activities; maintaining and developing external, public and private partnerships; and, overseeing all equipment and facilities assigned to or owned by the College.

Priority consideration will be given to complete applications received by October 15, 2007. The position begins July 1, 2008, or as soon thereafter as possible.

For a complete description and application information visit **website:http://www.mnsu.edu/humanres/employment.**

SANTA FE INSTITUTE

Postdoctoral Fellowship Opportunities at the Santa Fe Institute

The Santa Fe Institute (SFI) is selectively seeking applications for Postdoctoral Fellows for appointments begginning fall 2008.

Fellows are appointed for up to three years during which they pursue research questions of their own design and are encouraged to transcend disciplinary lines. SFI's unique structure and resources enable Fellows to collaborate with members of the SFI faculty, other Fellows, and researchers from around the world.

As the leader in multidisciplinary research, SFI has no formal programs or departments, and we accept applications from any field. Research topics span the full range of natural and social sciences and often make connections with the humanities. Most research at SFI is theoretical and/or computational in nature, although some research includes an empirical component in collaboration with other institutions.

Descriptions of the research themes and interests of the faculty and current Fellows can be found at http://www.santafe.edu/research.

BENEFITS: The compensation package includes a competitive salary and excellent health and retirement benefits. As full participants in the SFI community Fellows are encouraged to invite speakers, organize workshops and working groups and engage in research outside their field. Funds are available to support this full range of research activities.

REQUIREMENTS: SFI is known for its catalytic research environment and applicants must demonstrate the potential to contribute to this community. Candidates must have a Ph.D. (or expect to receive one by September 2008), an exemplary academic record, and a proven ability to work independently. We expect a demonstrated interest in multidisciplinary research and evidence of the ability to think outside traditional paradigms.

Applications are welcome from candidates in any country. Successful foreign applicants must acquire an acceptable visa (usually a J-1) as a condition of employment. Women and minorities are especially encouraged to apply.

TO APPLY: Please view the full position announcement and application instructions at http://www.santafe.edu/postdocapp08. For full consideration, please submit all application materials, including three letters of recommendation, electronically (preferred) or via post by **November 15, 2007**.

For further information, e-mail postdocinfo@santafe.edu.

SFI is an equal opportunity employer.

Tenure Track Faculty Positions in Developmental Biology

Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center invites applications for junior tenure-track faculty positions in the Program in Developmental Biology. Successful candidates will carry out independent research programs addressing problems in any aspect of Developmental Biology. Topics of particular interest include stem cell biology, gametogenesis and genetic mechanisms in development. Sloan-Kettering Institute offers a highly interactive and exciting research environment with outstanding infrastructure and resources to support research (www.ski.edu). New faculty will be eligible to hold graduate school appointments in the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences, the Weill Graduate School of Medical Sciences of Cornell University, as well as the Tri-Institutional MD/PhD Training Program.

Candidates should e-mail their application in PDF format to: **devbio@mskcc.org** by November 1, 2007. The application should include a Curriculum Vitae, a description of past research, a description of proposed research, and copies of three representative publications. Candidates should arrange to have three letters of reference sent by e-mail to: **devbio@mskcc.org** and by regular mail to: **Developmental Biology Search, c/o Ms. Tiffany Lennon, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 135, New York, New York 10065.** The letters should arrive by November 1, 2007. Inquiries may be sent to Ms. Lennon at: **devbio@mskcc.org** or to Dr. Kathryn Anderson, Chair, Developmental Biology Program, Sloan-Kettering Institute. Memorial Sloan-Kettering Cancer Center is an Equal Opportunity Employer.

Memorial Sloan-Kettering Cancer Center
The Best Cancer Care. Anywhere.
www.mskcc.org

ST. MARY'S UNIVERSITY

Fostering Academic Excellence And Spiritual Growth

ASSISTANT PROFESSOR OF BIOLOGICAL SCIENCES

St. Mary's University of San Antonio, a private Catholic university, invites applications for a full-time tenure-track faculty position in the Department of Biological Sciences beginning August, 2007. We are seeking a life scientist with expertise in an area of biology that will complement the current strengths of the department. Candidates with expertise in all fields of the life sciences are encouraged to apply, especially those with training and expertise in the areas of developmental biology, embryology, and/or molecular genetics. The primary responsibilities of this position will be teaching two courses with associated laboratory per semester. These courses will include introductory biology, as well as courses to be developed by the candidate in his/her area of specialty. While teaching is the primary function of the position, research, especially involving undergraduates, is expected of the successful candidate. The presence of an active biomedical research community in the San Antonio area provides the opportunity to establish collaborative research projects in many fields. A Ph.D. in biology or a related discipline is required, and postdoctoral experience is preferred. Founded in 1852 and operated by the Society of Mary, St. Mary's University is a Hispanic- serving institution with a proven history of preparing undergraduate science students for careers in health professions and research. For more information visit the university Web site at **www.stmarytx.edu;** or contact the chair at **cnolan@stmarytx.edu**; or call **210-436-3241**. Salary is commensurate with experience and is accompanied by a strong benefits package. All qualified applicants are welcome; minorities and women are encouraged to apply. Applicants should submit a letter of application detailing interest in the position and a description of teaching and professional development goals, a curriculum vitae, copies of graduate transcripts, the e-mail addresses and telephone numbers of references, and have three letters of recommendation sent to:

Dr. Colleen J. Nolan, Chair, Department of Biological Sciences, St. Mary's University, One Camino Santa Maria, San Antonio, TX, 78228-8511. Electronic submission of applications is encouraged; however, incomplete applications may not be considered. Review of applications will begin **November 2, 2007**, and will continue until a suitable candidate is identified. St. Mary's University is an Equal Opportunity Employer.

TEMPLE UNIVERSITY®

Faculty Positions in Ecology/ Environmental Biology

The Department of Biology at Temple University is expanding its faculty and anticipates adding several new faculty members in the next year. Applications for tenure-track faculty positions at all levels in the general field of Ecology and Environmental Biology are invited. Successful candidates should have a strong publication record and an innovative research program with level-appropriate external funding. Contribution to teaching at both the undergraduate and graduate levels is expected.

Applicants for junior positions with a Ph.D. and postdoctoral experience should send curriculum vitae, a description of research interests, a statement of teaching philosophy, and three letters of reference to: **Dr. Robert Sanders, Search Committee Chair, Department of Biology, Temple University, 1900 N. 12th St., Philadelphia, PA 19122.** Senior applicants should provide curriculum vitae and the names and contact information for references. Review of applications will begin October 15, 2007. Temple University is an equal opportunity, equal access, affirmative action employer committed to achieving a diverse community. AA, EOE, m/f/d/v.

POSITIONS OPEN

ASSISTANT/ASSOCIATE PROFESSOR
Department of Biochemistry and Molecular Biology
State University of New York
Upstate Medical University

We seek applications to fill one or two tenure-track positions at either the **ASSISTANT or ASSOCIATE PROFESSOR** levels from individuals studying fundamental molecular processes in eukaryotic organisms. We encourage applications in structural biology, genomics, membrane biology, and bioinformatics. The successful applicants will be expected to develop well-funded research programs and to contribute to medical and graduate teaching. We offer a highly competitive startup package and salary. Further information about the Department can be found at **website: http://www.upstate.edu/biochem.**

Candidates should have a Ph.D. or equivalent, postdoctoral experience, and a strong publication record. Applicants should e-mail a PDF file containing curriculum vitae, a summary of research accomplishments, and future research plans to **e-mail: biochem@upstate.edu.** In addition, three letters of reference should be mailed directly to: **Dr. Barry E. Knox, Search Committee Chair, Department of Biochemistry and Molecular Biology, 750 East Adams Street, Syracuse, NY 13210.**

Review of applications will begin on November 1, 2007, and continue until the positions are filled. *Women and minorities are highly encouraged to apply. Upstate Medical University is an Equal Opportunity/Affirmative Action Employer.*

UNIVERSITY of FLORIDA
FACULTY POSITION in CHEMISTRY

The Department of Chemistry at the University of Florida announces a search for a tenure-track faculty member, at the level of **ASSISTANT PROFESSOR,** to begin in fall 2008. Candidates with research interests in the general area of biochemistry are invited to apply, and applications in the areas of bioinorganic and metallobiochemistry will be of special interest. In addition to contributing to the research, teaching, and service missions of the Department of Chemistry, the successful candidate will have numerous opportunities for campus-wide interactions with faculty in the Colleges of Liberal Arts and Sciences, Medicine and Engineering, and other University-based centers and institutes, including the National High Magnetic Field Laboratory. Applicants should submit curriculum vitae, brief descriptions of their research plans, their graduate/undergraduate teaching interests, and arrange to have three letters of recommendation sent on their behalf to the: **Faculty Search Committee, Department of Chemistry, P.O. Box 117200, University of Florida, Gainesville, FL 32611-7200** on or before October 19, 2007. *The University of Florida is an Equal Opportunity Employer and welcomes nominations and applications from women and minority group candidates.*

CALIFORNIA INSTITUTE of TECHNOLOGY
Genetics of Neural Systems and Behavior

We invite applications for a tenure-track **ASSISTANT PROFESSOR** appointment in the Division of Biology at the California Institute of Technology. We are seeking highly qualified candidates who are committed to a career in research and teaching. The applicant should conduct research at the interface of molecular biology and systems neuroscience aimed at understanding neural circuits and the control of behavior. We encourage applications from individuals who may, but need not, work on conventional genetic model organisms, either vertebrate or invertebrate. Appointment is contingent upon completion of Ph.D.

Please submit online application at **website: http://www.biology.caltech.edu/Positions** and include a brief cover letter, curriculum vitae, relevant publications, and a description of proposed research. Instructions will be given for submissions of letters of reference when you apply online. *The California Institute of Technology is an Equal Opportunity/Affirmative Action Employer. Women, minorities, veterans, and disabled persons are encouraged to apply.*

POSITIONS OPEN

Washington University in St. Louis
SCHOOL OF MEDICINE

FACULTY POSITION in DEPARTMENT of CELL BIOLOGY and PHYSIOLOGY
Molecular Oncology Program

The Department of Cell Biology and Physiology at Washington University School of Medicine invites applications for a tenure-track appointment at the rank of **ASSISTANT PROFESSOR.** The successful candidate will join the Molecular Oncology Program, a joint program between the Departments of Cell Biology and Internal Medicine at Washington University School of Medicine. The Molecular Oncology Program is comprised of a vibrant group of interactive investigators studying cell cycle control, checkpoint control, cell death, G-protein signaling, telomere biology, HIV pathogenesis, metastasis, oncogenes, and tumor suppressors. Outstanding individuals investigating fundamental problems in molecular oncology are encouraged to apply. Candidates must demonstrate the ability to develop an independent research program and a commitment to excellence in graduate education. Applicants must have a Ph.D. and/or M.D. and postdoctoral experience. Please send curriculum vitae, a summary of current and proposed research programs, and arrange for three letters of recommendation to be sent to:

Drs. Helen Piwnica-Worms and Kendall J. Blumer, Co-Chairs
Cell Biology and Physiology Search Committee
Washington University School of Medicine
660 South Euclid Avenue - Campus Box 8228
St. Louis, MO 63110
E-mail: facultysearch@cellbiology.wustl.edu

Applications should be received by February 1, 2008. *Washington University is committed to increasing representation of women and members of minority groups on its faculty and particularly encourages applications from such candidates.*

UNIVERSITY of SOUTHERN CALIFORNIA
Physical Chemistry

The Department of Chemistry at the University of Southern California invites applicants for a tenure-track position in physical chemistry, at the level of **ASSISTANT or ASSOCIATE PROFESSOR,** to start in fall 2008. Candidates should have a Ph.D. and postdoctoral experience. We are interested in candidates in all areas of contemporary experimental physical chemistry. Interested candidates should send a cover letter, curriculum vitae, and a detailed description of research plans as PDF files to **e-mail: physsearch2007@chemmail.usc.edu.** In addition, three letters of recommendation should be sent to: **Professor Stephen Bradforth, Physical Chemistry Search Committee, Department of Chemistry, University of Southern California, Los Angeles, CA 90089-0482.** We will begin evaluation of applications on October 22, 2007. *USC values diversity and is committed to Equal Opportunity in Employment. Women and men, and members of all racial and ethnic groups are encouraged to apply.*

UNIVERSITY of CALIFORNIA, SANTA CRUZ

The Department of Earth and Planetary Sciences (EPS) seeks applicants for a **TENURE-TRACK POSITION** in geology. Position available: fall 2008. Open until filled. For full consideration, applications must be postmarked by December 1, 2007. For full details, see our **website: http://www.es.ucsc.edu/about/jobs/index.html.** Refer to position #357-08, or contact **Judy Van Leuven (e-mail: judy@pmc.ucsc.edu; telephone: 831-459-4478, website: http://www2.ucsc.edu/ahr/).**

Affirmative Action/Equal Employment Opportunity Employer.

POSITIONS OPEN

ASSISTANT PROFESSOR
Georgetown University Medical School

The Department of Biochemistry and Molecular and Cellular Biology invites applications for an Assistant Professor position (tenure track) in the field of proteomics data mining. The successful applicant should have a Ph.D. and postdoctoral training in computer science and bioinformatics, extensive experience in algorithm development for the analysis of mass spectrometry data, and should have a strong publication record in computer-based analysis of large scale proteomics data bases.

The successful candidate is expected to establish an active, extramurally funded research program that involves mentoring graduate students and to participate in the teaching of graduate and postgraduate classes in the Medical Center.

Please send curriculum vitae and a description of research interests along with the names of three individuals that can be contacted for letters of reference sent to: **Proteomics Search Committee, Department of Biochemistry and Molecular and Cellular Biology, Basic Science Building, Room 337, Georgetown University Medical School, 3900 Reservoir Road, N.W., Washington, DC 20057.**

Applications should be received no later than November 1, 2007.

Georgetown University Medical Center is an Equal Opportunity and Equal Access Institution.

BIOLOGY, ASSISTANT PROFESSOR. The Department of Biology at Shippensburg University invites applications for a tenure-track **PROKARYOTIC GENETICIST** position starting August 2008. Responsibilities include instruction of the following: a sophomore level genetics course, an upper-division undergraduate/graduate course in the area of candidate's specialty, and introductory courses for majors and nonmajors. The successful candidate will be expected to have a Ph.D. from an accredited institution completed by May 31, 2008. A successful demonstration of teaching effectiveness, a scholarly seminar, and evidence of a commitment to understanding diverse populations, will be required as part of the on-campus interview. Applicants should send curriculum vitae, copies of transcripts (both graduate and undergraduate), a brief statement of teaching philosophy and research interests, plus the names, addresses, and telephone numbers of three references to: **Dr. Sherri Bergsten, Biology Search Committee Chairperson, 1871 Old Main Drive, Shippensburg, PA 17257.** Review of application materials will begin on November 15, 2007, and will continue until the position is filled. *All applicants must furnish proof of eligibility to work in the United States upon appointment. Shippensburg University is an Equal Opportunity Employer.*

ASSISTANT PROFESSOR, PLANT BIOLOGY

The Department of Biological Sciences, California State University, Los Angeles, seeks to fill a tenure-track position in plant biology beginning fall 2008. A Ph.D. in biology, botany, or related field is required, with a minimum of one year of postdoctoral experience preferred. The candidate is expected to teach undergraduate and graduate courses, participate in program development, and establish an externally funded research program involving undergraduate and Master's students. The candidate is also expected to participate in University service, and to provide academic advisement to students. Submit curriculum vitae, research plans, statement of teaching philosophy, and three letters of reference to: **Search Committee Chair - Plant Biologist, Department of Biological Sciences, California State University, Los Angeles, 5151 State University Drive, Los Angeles, CA 90032 (e-mail: plapolt@exchange.calstatela.edu).** Review of completed applications will begin November 1, 2007, and may continue until position is filled. *EO/Title IX/ADA Employer. Qualified women and minorities are encouraged to apply.*

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Applicants must hold a PhD or equivalent doctoral-level degree in any physical, biological, medical/health, or social/behavioral science, or any engineering discipline. Individuals with a master's degree in engineering and three years of post-degree professional experience also may apply. Federal employees are not eligible and U.S. citizenship is required.

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The application deadline for the 2008-2009 fellowships is 20 December 2007. Fellowships are awarded in the spring and begin in September. Stipends range from $67,000 to $87,000.

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Krista Donaldson, PhD

Mechanical Engineering, Stanford University.

2004-2005 AAAS Fellow at the U.S. Department of State, Bureau of Near Eastern Affairs, Iraq Desk, Economic Section.

Now a research associate at Stanford University's Center for Design Research.

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POSITIONS OPEN

TWO ASSISTANT PROFESSOR POSITIONS CONSERVATION BIOLOGIST and VIROLOGIST

The Department of Biology and Marine Biology at the University of North Carolina, Wilmington, invites applications for two tenure-track positions starting August 2008.

Conservation Biologist: Candidates in any subdiscipline of conservation biology are encouraged to apply.

Virologist: Candidates in any area of virology are encouraged to apply; however, the successful candidate will teach courses in their area of expertise, immunology, or another health-related course.

Duties for both positions include undergraduate and graduate teaching, and maintaining an active research program that involves both graduate and undergraduate students. The Department offers a B.A. in biology, B.S. and M.S. degrees in biology and in marine biology, and a Ph.D. in marine biology. Modern laboratories and diverse core facilities are available in the Department and at the Center for Marine Science (**websites: http://www.uncw.edu/bio/** and **http://www.uncw.edu/cmsr/**). Candidates must have a Ph.D. and postdoctoral experience. To apply, complete the online application available at **website: http://consensus.uncw.edu.** The application package should include a letter of interest that must contain brief statements of teaching and research interests, curriculum vitae, and contact information for three references. M.S. Word and Adobe PDF documents are the preferred programs for attachments. The Chair of the Conservation Biologist Search is **Dr. Joseph Pawlik (e-mail: pawlikj@uncw.edu** or **telephone: 910-962-2377**), and the Chair of the Virology Search is **Dr. Ronald Sizemore (e-mail: sizemorer@uncw.edu** or **telephone: 910-962-2304**). For questions about the online application process, contact **Ms. Tracie Chadwick (e-mail: chadwickt@uncw.edu** or **telephone: 910-962-3536**). Application review will begin November 9, 2007. *Under North Carolina law, applications and related materials are confidential personnel documents and not subject to public release. UNCW conducts criminal background checks on finalists prior to offers of employment. The Department is dedicated to promoting diversity in education.*

UNC Wilmington is an Equal Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply.

BIOLOGIST/POPULATION GENETICIST

Hillsdale College, a selective and independent liberal arts college of 1,200 students in south central Michigan, is seeking a broadly trained Biologist/Population Geneticist. The successful candidate for this tenure-track position, at the **ASSISTANT PROFESSOR** rank, must demonstrate effective design and teaching of undergraduate classes from introductory nonmajors to upper-level biology majors, as well as an ability to supervise undergraduate senior thesis research. Teaching experience required, Ph.D. expected, and postdoctoral experience is desirable. Additional resources and position description can be found at the Department **website: http://www.hillsdale.edu/academics/majors/biology.asp.** Review of applications will begin on November 1, 2007. Starting date is August 2008. For additional information contact **Dr. Francis X. Steiner** by **telephone: 517-607-2399** or via **e-mail: fxs@hillsdale/edu.**

Send resume, including statements of teaching philosophy and research interests, three letters of recommendation, and transcripts to: **Dr. Francis X. Steiner, Chairman, Department of Biology, Hillsdale College, Hillsdale, MI 49242.** Applicants should familiarize themselves with the College's Mission Statement (**website: http://www.hillsdale.edu/about/history/mission.asp**) and include in their application letter a response to the mission, addressing their interest and ability to teach in the context of a liberal arts environment. *Equal Opportunity Employer.*

POSITIONS OPEN

University of Maryland
CENTER FOR ENVIRONMENTAL SCIENCE

CHESAPEAKE BIOLOGICAL LABORATORY

Tenure-track position with research focus on aquatic geochemical cycling, reactivity, and/or remediation of anthropogenic organic chemicals.

Applications are invited for a **FACULTY** member to develop strong research and graduate teaching program that complements existing faculty strengths in environmental toxicology and geochemistry, fisheries science, and ecosystem studies. Must have strong interest in interactive, collaborative work. Target date for applications: October 31, 2007. Full description and application information at **website: http://www.cbl.umces.edu.** *An Affirmative Action/Equal Opportunity Employer. We promote excellence through diversity and encourage women and minorities to apply.*

BRIDGEWATER STATE COLLEGE
Website: http://www.bridgew.edu

ASSISTANT PROFESSOR, DEPARTMENT of BIOLOGICAL STUDIES, TOXICOLOGY. The position requires helping the Department expand its biomedical concentration by offering upper-level electives in an area of toxicology, and one or more of the following: lecture and laboratory sections in cell biology, genetics, introductory biology courses, or first year seminars for majors and nonmajors. Also required are advising students and supporting the Department's strong program in undergraduate research.

Required minimum qualifications: The successful candidate must have an earned Ph.D. by May 2008, and excellent communication skills. Experience and strong interest in teaching nonmajors biology, undergraduate research, and an upper-level course in an area of toxicology are required.

Preferred qualifications: Postdoctoral experience and interest in bio-education outreach are preferred.

Applicants should be strongly committed to excellence in teaching and advising, and to working in a multicultural environment that fosters diversity. They should also have an ability to use technology effectively in teaching and learning, the ability to work collaboratively, evidence of scholarly activity, and a commitment to public higher education.

Special instructions to applicants: Please visit our career site and apply online, **website: https://jobs.bridgew.edu.** Submit a letter of interest, curriculum vitae, a statement describing teaching and research interests, and names, addresses, and telephone numbers of three professional references for this position. Review of applications will continue until the position is filled. For more information about employment at Bridgewater State College, please visit our **website: http://www.bridgew.edu/HR/JobList/.** To apply: Please apply online at **website: http://jobs.bridgew.edu.** *Bridgewater State College is an Affirmative Action/EqualOpportunity Employer which actively seeks to increase the diversity of its workforce.*

The METHODIST HOSPITAL RESEARCH INSTITUTE
Weill Cornell Medical College

Newly established Laboratory for Imaging Chemistry in Radiology Department develops novel imaging agents to sense molecular processes and disease-related targets, such as tumorigenesis, cardiovascular disease, inflammation, stem cell biology, and gene therapy. A **RADIOCHEMIST** is needed to overlook good manufacturing practice (GMP) synthesis of PET agents for clinical applications. Prior experience in GMP is required. Several **POSTDOCTORAL POSITIONS** in peptide chemistry, bioconjugation, fluorochrome chemistry, radiochemistry and nano technology are also available. To apply, please e-mail curriculum vitae and contact information of three references to **Dr. Ching H. Tung** at **e-mail: ctung@tmhs.org.**

POSITIONS OPEN

FACULTY POSITION for STEM CELL FACULTY RECRUITMENT
Department of Pharmacology University of Illinois at Chicago

The Department of Pharmacology at the University of Illinois College of Medicine (Chicago) is seeking candidates for an **ASSOCIATE PROFESSOR or PROFESSOR** appointment in the field of stem cell biology. Candidates should have a Ph.D. and/or M.D. degree, an outstanding publication record, and an NIH-funded research program in any on these areas: (1) stem cell biology, including cancer stem cells; (2) regenerative medicine; (3) molecular aspects of stem cell renewal/differentiation; (4) stem cell-based therapy. The Department has strong research and training programs (**website: http://www.uic.edu/depts/mcph/**) and consistently ranks among the top nationally. The successful candidate will have extensive opportunities for interdisciplinary collaboration, and a highly competitive startup package will be offered. Applications will be screened up to December 1, 2007. Position available July 2008. Please send by e-mail a single PDF file containing (1) curriculum vitae, (2) a summary of major research accomplishments and future research plan, (3) names, addresses, and e-mail addresses for three references to: **Attn: AP001 Search (e-mail: pharmjob@uic.edu), Department of Pharmacology (MC 868), University of Illinois at Chicago, College of Medicine, 835 S. Wolcott Avenue, Room E403, Chicago, IL 60612.** *UIC is an Affirmative Action/Equal Opportunity Employer.*

Multiple **POSTDOCTORAL ASSOCIATE POSITIONS** in microbiology are presently open in the School of Life Sciences at Arizona State University to study (1) microbial diversity and adaptations in desert soil communities, (2) molecular genetics of secondary metabolites, (3) metagenomic analyses of large-scale bioreactor communities, (4) genomic analyses of microbe-mineral interactions, and (5) metagenomic prospecting for biohydrogen production, all with particular emphasis in cyanobacterial systems.

Candidates must have earned a Ph.D. in microbiology or a related, appropriate field at the time of appointment. Experience with genomic analyses and molecular biology is required for all positions. Starting date is negotiable. Team candidacies will be given consideration. Competitive salary and benefit package. Interested candidates should send cover letter summarizing qualifications, experience and interests, position preference, curriculum vitae, up to three representative reprints, and names, addresses, and e-mail addresses of three references to: **Dr. Ferran Garcia-Pichel, School of Life Sciences, Arizona State University, P.O. Box 874501, Tempe, AZ 85287-4501.** Electronic submissions are acceptable **(e-mail: ferran@asu.edu).** Application deadline is November 15, 2006; if not filled biweekly until search is closed. *Arizona State University is an Affirmative Action/Equal Opportunity Employer.*

The Department of Biological Sciences at Rowan University has an opening for a full-time professional staff position to serve as **PRE-PROFESSIONAL ADVISOR.** The responsibilities of this position include advising undergraduates interested in applying to medical school or entering other health professions and acting as a liaison to the admissions offices of medical schools and other professional schools. In addition, the successful candidate will teach one course per semester in the Department. A strong interest in, and commitment to, excellence in undergraduate education is required. Applicants should have a Ph.D. in some area of biology or an equivalent medical degree. Applicants should submit curriculum vitae, statement on teaching and advising, contact information for three references, and copies of graduate transcripts to: **Luke Holbrook, Chair, Biological Sciences, Rowan University, 201 Mullica Hill Road, Glassboro, NJ 08028,** or electronically to **e-mail: holbrook@rowan.edu.** Review of applications will begin October 15, 2007. For more information on this position, go to **website: http://www.rowan.edu/jobs.**

Featured Employers

Search **ScienceCareers.org** for job postings from these employers. Listings updated three times a week.

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www.kellyscientific.com

Novartis Institutes for BioMedical Research
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COURSE

Practical Course on Genetic Engineering of the Mouse Genome to Understand Human Gene Function and Disease

January 11–21, 2008, in Valdivia, Chile

Centro de Estudios Científicos (CECS)

Applications are invited for an international course for graduate students, postdoctoral fellows, and junior faculty.

This intensive advanced course is for scientists working in the field of genetic engineering of the mouse genome. International authorities on genetic engineering and local investigators will cover general strategies and emerging approaches to develop and study transgenic and mutant mouse models. Conducted in English, practical classes on the creation and analysis of transgenic and mutant mice will be held in the mouse barrier facility of CECS and its laboratories.

Application deadline: October 25, 2007

More information: www.hhmi.org/grants/courses

Sponsors: Howard Hughes Medical Institute and Centro de Estudios Científicos

POSITIONS OPEN

Panacos

Senior/Principal Scientist – Virology

Panacos Pharmaceuticals is a clinical-stage, public biopharmaceutical company engaged in the discovery and development of novel therapeutics for HIV and other serious viral diseases. We are currently seeking an experienced virologist at the Senior/Principal Scientist level to join our research team in Gaithersburg, MD. The successful candidate will be responsible for characterizing the activity and mechanism of action of novel antiviral compounds discovered as part of the company's HIV maturation inhibitor program. The individual will also provide clinical virology support to the company's clinical programs and may contribute to additional antiviral programs as the company expands. Requirements include a Ph.D. in a biological discipline with a strong background in virology, excellent communication skills, and excellent skills in molecular biology, biochemistry, and cell biology. Preference will be given to candidates with relevant postdoctoral experience, especially those with experience in antiviral drug discovery/development. Experience managing other researchers a plus. Individuals with a background in retroviral assembly/maturation and experience working with HIV are strongly encouraged to apply. Responsibilities, title, and compensation commensurate with experience. Send resume to: **hr@panacos.com** or fax **617-923-2529**.

AWARDS

Harold M. Weintraub Graduate Student Awards – 2008

The Fred Hutchinson Cancer Center is seeking nominations for outstanding Graduate Students for the Harold M. Weintraub Graduate Student Award to recognize outstanding achievement during Graduate Studies in the Biological Sciences. Awardees will participate in a scientific symposium honoring Hal Weintraub and his commitment to innovative science.

The ninth annual Award Symposium will be held May 2-3, 2008. Graduate Student Awardees will be selected from among those nominated on the basis of quality, originality, and significance of their work, as well as to represent a diverse range of research topics. The Hutchinson Center Weintraub and Groudine Fund, established to foster intellectual exchange through the promotion of programs for graduate students, fellows and visiting scholars, will cover expenses for the Graduate Student Awardees.

One nomination may be submitted per Department or Program. The nomination should be submitted by the Department or Program Chairperson and include the student's CV, a one page description of the thesis work conducted, and a recommendation letter from the student's mentor. Additional information concerning the Award and nomination process can be found at the website listed below.

The nomination should be submitted **ONLINE** by **December 15, 2007** -- following the instructions at the website: **http://www.fhcrc.org/science/basic/weintraub/**

Questions regarding this Award should be addressed to **Susan Parkhurst** (**susanp@fhcrc.org**).

CONFERENCE

Conference on Biology and Politics

NSF Funded

Host:
University of Illinois at Urbana-Champaign

March 7-8, 2008

Ethnic minorities, junior faculty, and advanced graduate students are encouraged to initiate correspondence.

Forward inquiries to:
Ira H. Carmen,
Department of Political Science
icarmen@uiuc.edu

Gene E. Robinson,
Department of Integrative Biology
generobi@uiuc.edu

ILLINOIS
UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

Announcement

POSITIONS OPEN

NAVAL RESEARCH LABORATORY
Nanoscience and Nanotechnology

The Research Scientist selected for this employment opportunity will join a diverse group of physicists, mathematician, chemists, and electrical and mechanical engineers exploring new nano-fabrication approaches using thin film materials to create large systems of coupled nano-mechanical resonators, studying their dynamic mechanical, elasto-optic, and transport properties, and exploiting such systems for new device technologies. Candidates should apply who have a strong background and interest in the area of nano-science and nano-technology as related to the design and conduct of state-of-the-art measurements related to the elastic, elasto-optic, and transport properties of existing, emerging, and future nano-structures, particularly those of silicon and diamond implemented as large arrays of coupled nano-mechanical resonators. The experimental studies would involve optical pumping and thermal-elastic drive techniques, measurement of the parameters that control the elastic response and transport properties of the array, and calorimetric measurements at low and ultra low temperatures.

This position will be filled at Career Level IV (equivalent to GS-14-15). Salary will be determined based upon selectee's background, experience, and market considerations.

Announcement opens October 1, 2007, and closes October 31, 2007.

Applicants are encouraged to visit the websites. For those applicants with status (i.e., current government employees on a competitive career or career-conditional appointment, reinstatement eligibles, Veterans Employment Opportunities Act eligibles, et cetera), apply to vacancy announcement number NE7-1310-04-K9675064-I. For applicants without status, apply to vacancy announcement number NE7-1310-04-NRL0618-DE.

Follow instructions regarding how to apply for each **website: https://chart.donhr.navy.mil** and click on search for jobs, type in announcement number and press enter to obtain qualification information and instructions on how to apply.

The Naval Research Laboratory is an Equal Opportunity Employer.

The NCI-designated Cancer Center of the Burnham Institute for Medical Research seeks independent investigators with research programs in cancer stem cell biology, epigenetics, and tumor microenvironment. Individuals at any career level, but especially junior investigators, are encouraged to apply. Burnham offers an outstanding and highly collaborative research environment, supported by a wide range of shared resources. For more details visit our **website: http://www.burnham.org.** Informal inquiries should be directed to appropriate **Cancer Center Program Directors.** To apply, please submit curriculum vitae and research summary electronically by November 1, 2007, to **e-mail: ccrecruit@burnham.org.** Candidates should arrange to have three letters of reference sent by **e-mail: ccrecruit@burnham.org** or regular mail to: **Cancer Center Recruit Committee, c/o Kristiina Vuori, M.D., Ph.D., NCI Cancer Center, Burnham Institute for Medical Research, 10901 North Torrey Pines Road, La Jolla, CA 92037.** *Equal Opportunity Employer/Affirmative Action.*

ANATOMY and CELL BIOLOGY

The Department of Anatomy and Cell Biology, Indiana University School of Medicine, invites applications for up to two tenure-track faculty positions at the **ASSISTANT or ASSOCIATE PROFESSOR** levels starting July 2008. The successful applicant will have an active research program preferably in such areas as stroke/cerebral ischemia, spinal cord regeneration/repair, skeletal biology, or polycystic kidney or renal stone disease. Teaching in medical neuroscience or histology is preferred. Information about the Department and faculty is available at **website: http://anatomy.iupui.edu.** Send curriculum vitae, personal statement, and names and addresses of three references electronically (PDF format) by December 15, 2007, to: **Joan Charlesworth (e-mail: jocharle@iupui.edu).** *Affirmative Action/Equal Opportunity Employer; Minorities/Females/Persons with Disabilities.*

FACULTY POSITIONS in BIOLOGY
The University of Washington

The University of Washington's Department of Biology has two open tenure-track faculty positions. We welcome applicants in both core and interdisciplinary areas of biology but have particular interest in areas of cellular, molecular, and physiological levels of organization in plants or animals. A record of outstanding achievement, a promising research program, and a commitment to teaching are more important than the specific research area. Our consolidation of Botany, Zoology and Undergraduate Biology Programs into a single unit expands opportunities for new projects and interdisciplinary initiatives. Information about the Department is available at **website: http://www.biology.washington.edu.**

Appointments at the **ASSISTANT PROFESSOR** rank are anticipated. Appointments at the **ASSOCIATE or FULL PROFESSOR** rank may be considered for candidates who have demonstrated a commitment to mentoring underrepresented students in the sciences. Applicants must have earned a Doctorate by the date of appointment.

Please apply online at **website: http://www.biology.washington.edu/fachires/** and submit a cover letter, curriculum vitae, sample reprints, statements of research and of teaching interests, and names of at least three references. Applications received by November 1, 2007, will be given priority.

University of Washington faculty engage in teaching, research, and service. The University of Washington, a recipient of the 2006 Alfred P. Sloan award for Faculty Career Flexibility, is committed to supporting the work-life balance of its faculty. *The University is building a culturally diverse faculty and staff and strongly encourages applications from women, minorities, individuals with disabilities, and covered veterans. The University of Washington is an Affirmative Action, Equal Opportunity Employer.*

ASSISTANT/ASSOCIATE/FULL PROFESSOR (VIROLOGIST/TENURE TRACK)
Department of Biological Sciences

The Department of Biological Sciences at Louisiana State University, **website: http://www.biology.lsu.edu,** invites applications for an Assistant/Associate/Full Professor (virologist/tenure track) position. Required qualifications: Ph.D. or equivalent degree in biological sciences or a related field, postdoctoral experience, record of creative and significant research in any area of virology (mammalian model systems preferred), and/or host responses to viral infection. Responsibilities: develops a vigorous, extramurally funded research program and contributes to undergraduate and graduate teaching. Salary and level are commensurate with experience. An offer of employment is contingent on a satisfactory pre-employment background check. Application deadline is November 1, 2007,or until a candidate is selected. Send curriculum vitae (including e-mail address), statement of research and teaching interests, three letters of recommendation and reprints of key publications to:

Virology Search Committee
Department of Biological Sciences
202 Life Sciences Building
Louisiana State University
Reference: #023966
Baton Rouge, LA 70803

LSU is an Equal Opportunity/Equal Access Employer. We encourage applications from women and minorities.

FACULTY POSITION
DEPARTMENT CHAIR

Seeking applications for Department Chair position at the rank of **FULL PROFESSOR** in the Department of Biological Sciences, California State University, Long Beach starting fall 2008; see **websites: http://www.csulb.edu/divisions/aa/personnel/jobs/cnsm** or **http://www.csulb.edu/depts/biology** for application details and additional information. Application review begins on November 2, 2007. *CSULB is an Equal Opportunity Employer committed to excellence through diversity, and takes pride in its multicultural environment.*

ANIMAL PHYSIOLOGIST
ASSISTANT PROFESSOR

A tenure-track opening for an Animal Physiologist is available in the Department of Biological Sciences at DePaul University starting September 2008. Successful candidate will be broadly trained in animal physiology with a strong commitment to undergraduate education. All subdisciplines and animal model systems will be considered. Ph.D. required; postdoctoral and previous teaching experience preferred. Teaching responsibilities to include some combination of: introductory biology for nonmajors; co-teaching one quarter of introductory biology sequence for majors; vertebrate physiology; and graduate/advanced undergraduate course in candidate's area of expertise. Startup funds are provided. The Department is housed in a spacious and well-equipped teaching, research, and support facility, including a 2,000 square-feet, state-of-the-art staffed animal care facility. Review of applications will begin November 1, 2007, and will continue until position is filled. Please send: curriculum vitae; three letters of reference; statement of research interests; statement of educational philosophy and teaching interests; and general list of equipment and supply needs with cost estimates to: **Animal Physiology Search Committee, Department of Biological Sciences, DePaul University, 2325 N. Clifton Avenue, Chicago, IL 60614.** Additional inquiries to above address, or **fax: 773-325-7596; e-mail: jdean@depaul.edu.** *The Department of Biological Sciences seeks diversity in its faculty. We encourage applications from women, people of color, and the members of other historically underrepresented groups. DePaul University is committed to diversity and equality in education and employment.*

ASSISTANT PROFESSOR, University of California, Davis. Tenure-track faculty position associated with the Foods for Health Initiative in Department of Chemical Engineering and Materials Science and Department of Food Science and Technology in biochemical engineering, biomaterials, biophotonics, food engineering, biochemistry, or a related field. Applicants are expected to hold a Ph.D. in a relevant area. Apply at **website: http://www.chms.ucdavis.edu/employment/.** The position is open until filled; but to assure full consideration, submit applications no later than December 3, 2007. Start date of July 1, 2008. *UC Davis is an Affirmative Action/Equal Employment Opportunity Employer and is dedicated to recruiting a diverse faculty community. We welcome all qualified applicants to apply, including women, minorities, individuals with disabilities and veterans.*

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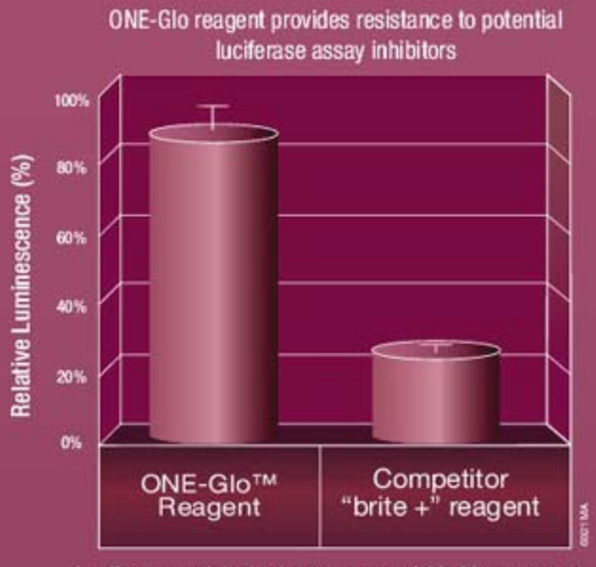

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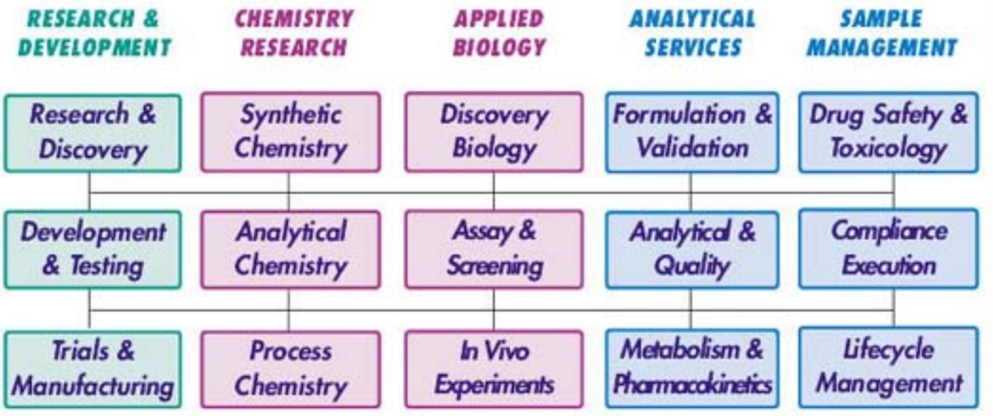

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